BEDAQUILINE DONATION PROGRAM

Asia Regional Pharmacovigilance Workshop: Implementation of active TB drug-safety monitoring and management for new drugs and treatment regimens for multidrug-resistant tuberculosis

Hosted by USAID Control and Prevention of Tuberculosis Project (CAP-TB) and FHI 360

25-27 April 2017
Bangkok, Thailand

USAID FROM THE AMERICAN PEOPLE

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CAP-TB CONTROL AND PREVENTION OF TUBERCULOSIS

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Executive Summary

The USAID Control and Prevention of Tuberculosis Project (CAP-TB) convened key stakeholders from Burma, China, India, Indonesia, Pakistan, Papua New Guinea, Philippines, South Korea, Thailand and Vietnam for the Bedaquiline Donation Program's Asia Regional Pharmacovigilance Workshop from 25 to 27April 2017 in Bangkok, Thailand.

The World Health Organization (WHO) recommends that countries introducing ND and STR for DR-TB should develop and implement a system for active pharmacovigilance (PV) that allows for the detection, reporting and management of adverse drug reactions (ADRs). It is anticipated that programs that are actively monitoring and managing ADRs are more likely to achieve better treatment outcomes. In 2015, WHO released its aDSM framework, which describes how to implement active PV in order to quickly detect, manage and report suspected or confirmed drug toxicities within the context of ND and STR. Now, many countries are introducing ND and STR for DR-TB, uncovering challenges in understanding and properly implementing aDSM.

The workshop aimed to gather countries in the Asia Pacific, enabling experiences sharing on pharmacovigilance for drug-resistant tuberculosis (DR-TB). Specifically, countries received technical updates on aDSM approaches and shared their progress on implementing active TB drug-safety monitoring and management (aDSM) for new TB drugs and treatment regimens. Also, countries has been able to develop national roadmap for aDSM implementation through the interagency collaboration. It was organized as part of the USAID-Janssen Bedaquiline donation program's technical assistance to strengthen capacity of countries that are introducing new drugs (ND) and shorter treatment regimens (STR), with the goal to improve monitoring of patients' safety and to standardize adverse event reporting using the World Health Organization's aDSM framework.

The key objectives of the workshop were:

1. Engage TB stakeholders of the ten participating countries on the need for stronger PV systems to ensure patients' safety and appropriate use of ND/STR.
2. Develop country roadmaps, actions and standard operating procedures (SOPs) for aDSM implementation in country settings.
3. Identify opportunities and consensus for the national drug regulatory agencies (NDRA) and national TB programs (NTP) to help facilitate effective collaboration and joint implementation of aDSM activities.
4. Present and share experiences and lessons learned from countries that have implemented aDSM as part of the introduction of ND/STR implementation for DR-TB care.
5. Discuss the introduction of the WHO-recommended aDSM framework in the countries as part of ND/STR introduction.

By the end of the workshop, each country developed an aDSM roadmap which will guide planned and ongoing activities for aDSM supporting the introduction and scale-up of ND and STR. The roadmap will be used as a tool to strengthen coordination and partnership across all stakeholders and organizations to ensure that eligible patients are able to access ND/STR and that aDSM systems and reporting structures are established and strengthened. Countries aDSM road maps covers the five key components of the aDSM approach (adapted from the WHO aDSM framework)- the national coordination, policy guidelines and implementation plan development, recording and reporting structure, health care workers capacity development, clinical management and data management and analysis. The aDSM road map will be used to assess countries technical assistant needed and to measure progress in by the end of 2019.

Abbreviations and acronyms

ADR	adverse drug reaction
aDSM	active tuberculosis drug-safety monitoring and management
AE	adverse event
AMR	antimicrobial resistance
ART	antiretroviral therapy
BDQ	bedaquiline
CA	causality assessment
CAC	computer assisted coding
CDC	Centers for Disease Control and Prevention
CEM	cohort event monitoring
CIOMS	Council for International Organizations of Medical Sciences
CU Program	Compassionate Use Program
DLM	delamanid
DR-TB	drug-resistant tuberculosis
DS-TB	drug-sensitive TB
DST	drug susceptibility testing
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis and Malaria
GTB	WHO Global TB Programme
HCW	healthcare workers
ICSR	individual case safety report(s) (spontaneous reports)
IRD	Interactive Research & Development
KNCV	KNCV Tuberculosis Foundation, Netherlands
LIH	Luxembourg Institute of Health
LPA	line probe assay
LTFU	loss to follow-up
MDR-TB	multidrug-resistant tuberculosis
MSF	Médecins Sans Frontières

MSH	Management Sciences for Health
MTB	Mycobacterium tuberculosis
MTCs	Medicine and Therapeutic Committees
NADFC	National Agency of Food and Drug Control
NAP	National Action Plan for Combating MDR-TB
NCTLD	National Center for Tuberculosis and Lung Diseases, Georgia
ND	new drugs
NDOH	National Department of Health
NDRA	National Drug Regulatory Agency
NPV	national pharmacovigilance system
NTP	national TB program
PIH	Partners in Health
PLHIV	people living with HIV
PMDT	programmatic management of drug-resistant TB
PTA	patient triage application
PV	pharmacovigilance
PViMS	Pharmacovigilance Information Monitoring System
QTcF	QT correction formulas
rGLC	regional Green Light Committee
R&R	recording and reporting
RR-TB	rifampicin-resistant TB
SAE	serious adverse event
SIAPS	System for Improved Access to Pharmaceuticals and Services
STR	shortened treatment regimen
STREAM	shortened standardized treatment regimen of anti-tuberculosis drugs for patients with multidrug-resistant tuberculosis
TB	tuberculosis
TDR	Special Programme for Research and Training in Tropical Diseases
UNION	International Union Against Tuberculosis and Lung Disease
UMC	Uppsala Monitoring Center
URC	University Research Company, LLC
USAID	United States Agency for International Development
XDR-TB	extensively drug-resistant tuberculosis
WHO	World Health Organization

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SECTION I

Policy and Clinical Updates on New Drugs for MDR-TB

SECTION 1

Policy and Clinical Updates on New Drugs for MDR-TB

USAID vision

- Introduce bedaquiline (BDQ) as part of strengthening the quality of DR-TB management
- Countries ensure that all required elements from the WHO (Policy Implementation Package)[1] are in place and implemented
- Technical assistance and support will be provided to assist countries with the rapid implementation of the required elements and prevent delay to accessing BDQ

Workshop Objectives and Expectations and Outcomes[1]

Objectives

1. Engage TB stakeholders of the ten participating countries on the need for stronger PV systems to ensure patients' safety and appropriate use of new drugs (ND) and shorter treatment regimens (STR).
2. Develop country roadmaps, actions and standard operating procedures (SOPs) for aDSM implementation in country settings.
3. Identify opportunities and consensus for the national drug regulatory agencies (NDRA) and national TB programs (NTP) to help facilitate effective collaboration and joint implementation of aDSM activities.
4. Present and share experiences and lessons learned from countries that have implemented aDSM as part of the introduction of ND/STR implementation for DR-TB care
5. Discuss the introduction of the WHO-recommended aDSM framework in the countries as part of ND/STR introduction.

Expectations and outcomes

- Develop a clear understanding of the application and implementation of the aDSM framework at the country level in order to strengthen national PV systems related to ND/STR
- Achieve consensus on the reporting mechanisms of adverse drug reactions (ADRs), including Serious Adverse Events (SAEs), from the patient level to the level of NDRAs and the international community
- Implement the aDSM roadmap and identify concrete steps and actions for all organizations involved in aDSM implementation for achieving international standards in PV

[1] Policy Implementation Package for new TB drug introduction. WHO/HTM/TB/2014.22 at: http://who.int/tb/PIPnewTBdrugs.pdf

Table 1. Technical assistance to be provided directly by USAID and in collaboration with partners or World Health Organization

TECHNICAL ASSISTANCE

USAID direct support	Collaboration with Partners	Collaboration with WHO
• Challenge TB[2] • System for Improved Access to Pharmaceuticals and Services (SIAPS ending)[3] • Bilateral projects • Independent MDR-TB consultants • Global Fund TB Advisors to NTPs	• endTB Project[4] (Médicins Sans Frontières (MSF)/ Partners in Health (PIH) / Interactive Research & Development (IRD)) • The UNION	• WHO Regional Green Light Committee (rGLC) plays an important role for PMDT activities, including NDs and STR

Source: "Bedaquiline Donation Program Asia Regional Pharmacovigilance (PV) Workshop: Implementation of active TB drug-safety monitoring and management (aDSM) for New Drugs and treatment regimens for MDR-TB", presented by Dr. Edmund Rutta, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand.

Status of the introduction and roll out of new drugs and shortened course regimen for DR-TB treatment.

In 2015, approximately 580,000 persons developed MDR-TB or rifampicin-resistant (RR) TB worldwide, of which only 125,000 persons were initiated on treatment.[5] Given that only approximately 20% of all estimated MDR-TB patients start treatment, and of that about half experience unfavorable treatment outcomes, the U.S. Government launched the five-year *National Action Plan for Combating Multidrug-Resistant Tuberculosis (National Action Plan)* in December 2015.[6] The *National Action Plan* works domestically and internationally to contribute to the prevention, detection, and control of multidrug-resistant tuberculosis in an effort to avert tuberculosis-associated morbidity and mortality and support a shared global vision of a world free of tuberculosis.[2]

The goals of the *National Action Plan* are to:

- Strengthen domestic capacity to combat MDR-TB
- Improve international capacity and collaboration to combat MDR-TB
- Accelerate basic and applied research and development to combat MDR-TB

[2] https://www.challengetb.org/about

[3] http://siapsprogram.org/

[4] http://www.endtb.org/about

[5] http://www.who.int/tb/publications/global_report/en/

[6] https://www.usaid.gov/what-we-do/global-health/tuberculosis/national-action-plan-combating-mdr-tb

National Action Plan Targets

BY 2016

- Initiate appropriate treatment in 25% of patients with MDR-TB in 10 countries with the highest burdens of MDR-TB

BY 2018

- Initiate appropriate treatment in 35% of patients with MDR-TB in 10 countries with the highest burdens of MDR-TB

BY 2020

- Reduce by 15% the number of cases of MDR-TB in the United States
- Initiate appropriate treatment in 50% of patients with MDR-TB in 10 countries with the highest burdens of MDR-TB
- Reduce global TB incidence by 25% compared to 2015 levels
- Successfully treat at least 16 million TB patients in high-burden countries
- Achieve and maintain treatment success rates of 90% for individuals in high-burden countries with drug-susceptible TB

Source: "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand.

Introduction and scale up of ND/STR

The WHO approved the shorter MDR-TB treatment regimen[3] (STR) on 12 May 2016, and recommended that this shorter regimen of 9-12 months may be used instead of a conventional regimen in patients with rifampicin-resistant TB (RR-TB) or MDR-TB, who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely.[4]

The recommendation applies to adults, children and people living with HIV (PLHIV); however, the STR is not recommended in case of second-line drug resistance, extrapulmonary disease and pregnancy. The STR will be monitored for effectiveness, relapse, and adverse events (approved for programmatic introduction supported by aDSM) and is also currently being evaluated by the STREAM Study, a clinical trial.

In mid-2016, USAID developed a guide for missions and implementing partners to support the STR's global scale-up, following the WHO's endorsement of the regimen as the first choice for RR-TB and MDR-TB. In March 2017, the WHO and Global Fund issued a memorandum supporting STR and appealed for urgent scale up within the new funding cycle. Starting in 2017, many countries plan to initiate patients on STR with rapid scale-up in 2018.[5]

Bedaquiline Donation Program in partnership with Johnson and Johnson

Background on bedaquiline and the donation program[6]

Bedaquiline (BDQ) was developed by Janssen Pharmaceuticals (a subsidiary of Johnson & Johnson) to treat MDR-TB, and it was approved in December 2012 by the US Food and Drug Administration. At that time, BDQ was the first new drug in a new class of antibiotics for TB to be approved in more than 40 years. In December 2014, USAID and the Johnson & Johnson affiliate, Janssen Therapeutics signed a Memorandum of Understanding for the Bedaquiline Donation Program, which was launched in April 2015. The goal of this donation program is to assist governments and patients to combat DR-TB by ensuring access to BDQ for the management of DR-TB.

The BDQ Donation Program removed price as a potential barrier to scale up accessibility, providing the drug to patients in low and middle income countries. The donation program provides 30,000 six-month courses of BDQ over four years (April 2015-2019) to the Global Drug Facility (GDF) – a $30 million value – for eligible patients in 100 low- and middle-income countries for appropriate use in accordance with WHO Guidelines.

Table 2. General provisions of the Bedaquiline Donation Program

Eligibility	Access	Adverse Events
• All countries on Global Fund (GF) 2016 Eligibility List and • Eligible for U.S. foreign assistance	• BDQ is available through the Stop TB Partnership's GDF • Countries are responsible for estimating the number of patients eligible for BDQ	• USAID and Janssen will collaborate with countries and partners to advance early detection and timely reporting of SAEs related to BDQ

Source: "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand.

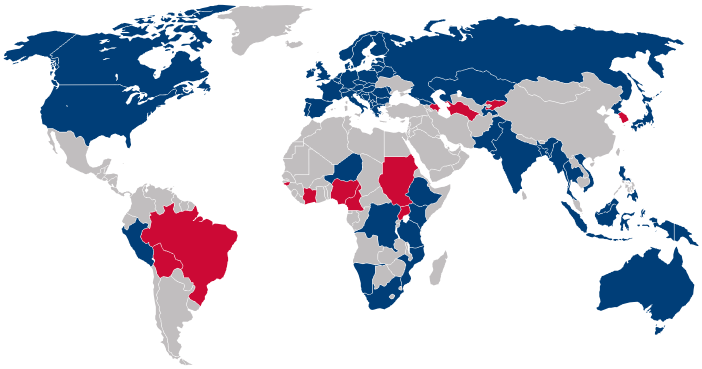


Figure 1. Global bedaquiline (BDQ) utilization

- Countries using bedaquiline under program conditions
- Countries awaiting arrival of bedaquiline to begin under program conditions

Source: "Programmatic introduction of newer drugs for drug-resistant tuberculosis: Overview, clinical considerations, ethical issues, and informed consent", via DR-TB STAT, presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 25 April 2017, Bangkok, Thailand.

As of end March 2017, a total of 8,874 patients were receiving BDQ through programmatic use and more than ten countries were awaiting arrival of BDQ to begin under program conditions.

Delamanid (DLM) updates

1. **Effective from** **1 March 2016,** DLM has been available for purchase via the StopTB/GDF
2. **Price is** **USD 1,700** for a full six-month treatment course
3. **More than** **100 countries** are eligible for TB financing by the Global Fund
4. **DLM** has been added to the GDF Strategic Rotating Stockpile
5. **Same order process** as for **BDQ**
6. **Same aDSM requirements** as for BDQ: reports must be filed via **GDF**
3. **As of October 2016,** DLM may be used in **patients 6-17 years**

Sources: "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand; "WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens", presented by Dennis Falzon, WHO/HQ Global TB Programme, Geneva, 25 April 2017, Bangkok, Thailand.

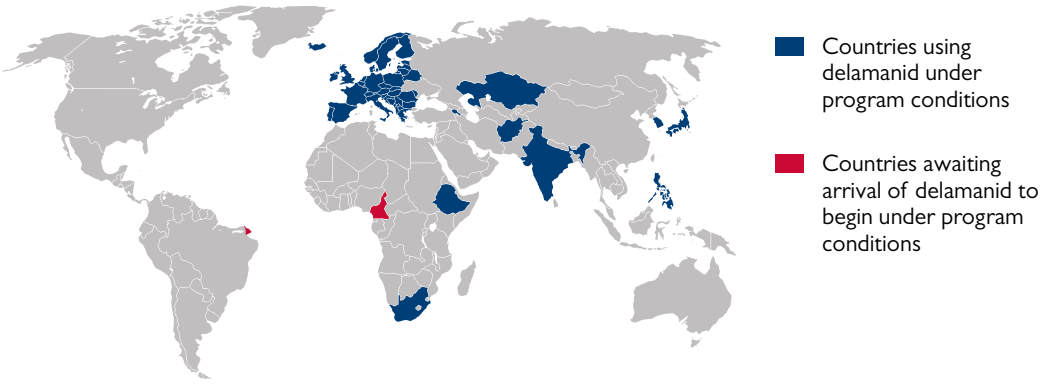
Summary of Updates for BDQ in 2017 from the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis[7]

- Adult MDR-TB patients not eligible for the newly WHO-recommended shorter regimen include
  - patients with additional resistance or intolerance to fluoroquinolones or second line injectable drugs
  - patients with extended pulmonary lesions, advanced disease and others deemed at higher baseline risk for poor outcomes
  - XDR-TB
- Bedaquiline can be used when an effective WHO-recommended longer regimen (~20- month total treatment duration) containing at least four second-line drugs in addition to pyrazinamide cannot be designed.
- BDQ must not be added alone to a failing regimen
- Healthcare authorities should set up an informed decision-making process that enables patients to make a duly informed decision regarding the use of bedaquiline.
- Bedaquiline shall be used for a duration of 6 months and at suggested dosing (400 mg daily for the first two weeks, followed by 200 mg three times per week for the remaining 22 weeks), preferably at the start of a longer regimen, which usually is given for at least 20 months (2). There is limited evidence, so far, to warrant its use beyond 6 months. BDQ has been used in adolescents; however, the data are insufficient to make any recommendations
- Settings introducing bedaquiline for MDR-TB treatment require active TB drug safety monitoring and management (aDSM) (21).
- Clinical monitoring and management of co-morbidities (especially cardiac and liver disease) should be in place.
- Baseline testing and monitoring for QT prolongation and for dysrhythmias are imperative.

Sources: World Health Organization. "Report of the Guideline Development Group Meeting on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. A review of available evidence (2016)." World Health Organization (2017).

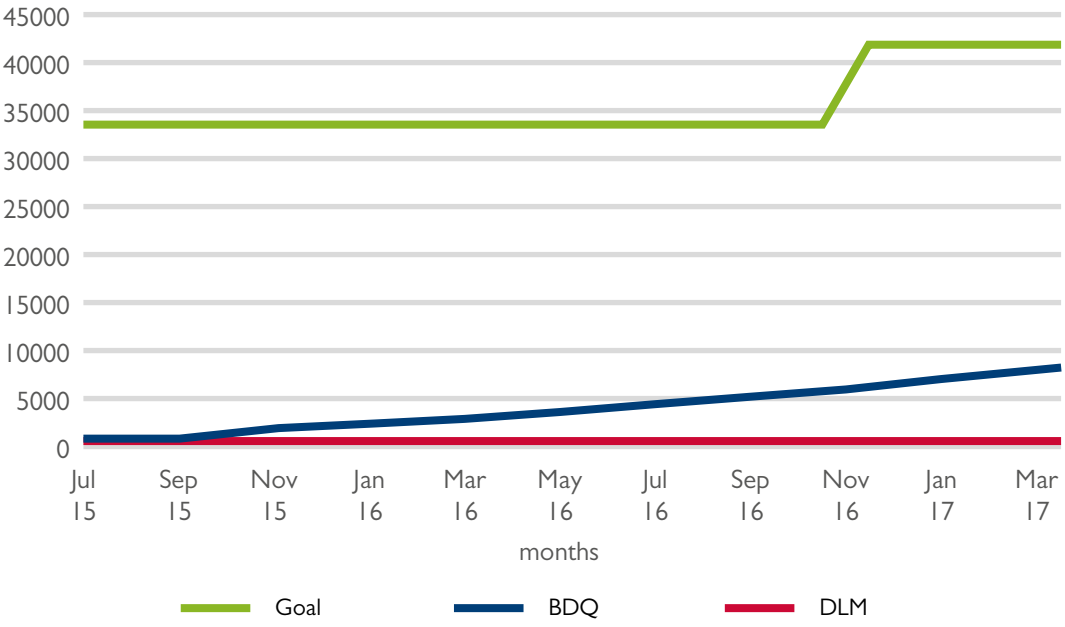
[7] To see the full meeting report go to : http://apps.who.int/iris/bitstream/10665/254712/1/WHO-HTM-TB-2017.01-eng.pdf

Figure 2. Global delamanid utilization



Source: "Programmatic introduction of newer drugs for drug-resistant tuberculosis: Overview, clinical considerations, ethical issues, and informed consent", via DR-TB STAT, presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 25 April 2017, Bangkok, Thailand.

Figure 3. Cumulative BDQ and DLM use



Note: Evidence base for current second-line drugs used for DR-TB comes from observational cohorts and meta-analyses.

Source: "Programmatic introduction of newer drugs for drug-resistant tuberculosis: Overview, clinical considerations, ethical issues, and informed consent", via DR-TB STAT, presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 25 April 2017, Bangkok, Thailand.

Five conditions for the inclusion of BDQ or DLM in the adult treatment regimen of MDR-TB[7]

1. Treatment administered under closely monitored conditions
2. Proper patient inclusion
3. Patient informed consent obtained
4. Adherence to principles of designing a WHO-recommended MDR-TB regimen
5. Pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions

In addition to BDQ and DLM, a number of repurposed drugs for DR-TB – drugs with indications for diseases other than TB – can potentially improve patient outcomes, in particular for XDR-TB. However, repurposed drugs are not always readily accessible to treat patients, and several barriers to wider use remain, including cost, regulatory issues and a lack of incentives for industry to promote access.[8]

Table 3. New and repurposed medicines recommended for the treatment of RR-TB and MDR-TB

A **Fluoroquinolones**[2]		Levofloxacin	Lfx
		Moxifloxacin	Mfx
		Gatifloxacin	Gfx
B **Second-line injectable agents**		Amikacin	Am
		Capreomycin	Cm
		Kanamycin	Km
		(Streptomycin)[3]	(S)
C **Other core second-line agents**[2]		Ethionamide/Prothionamide	Eto/Pto
		Cycloserine	Cs/Trd
		Linezolid	Lzd
		Clofazimine	Cfz
D **Add-on agents** (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide	Z
		Ethambutol	E
		High-dose isoniazid	H^h
	D2	Bedaquiline	Bdq
		Delamanid	Dlm
	D3	*p*-aminosalicylic acid	PAS
		Imipenem-cillastatin[4]	Ipm
		Meropenem[4]	Mpm
		Amoxicillin-clavulanate[4]	Amx-Clv
		(Thioacetazone)[5]	(T)

Source: "Programmatic introduction of newer drugs for drug-resistant tuberculosis: Overview, clinical considerations, ethical issues, and informed consent", presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 25 April 2017, Bangkok, Thailand.

The active TB drug-safety monitoring and management (aDSM) for New Drugs and Treatment Regimens for MDR-TB and Pharmacovigilance (PV) and WHO recommendations

What is Pharmacovigilance?

Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[9] PV aims to enhance patient care and patient safety in relation to the use of medicines, and to support public health programs by providing reliable and balanced information for the effective assessment of the risk-benefit profile of medicines.[10]

What is aDSM?

The term aDSM refers to the active and systematic clinical and laboratory assessment of patients while on second-line treatment for drug-resistant TB with new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens, in order to detect, manage and report suspected or confirmed drug toxicities. The overall objectives of aDSM are to ensure the safety of patients on second-line treatment for DR- TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines.[11]

Three essential aDSM components

1. Clinical monitoring: active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs
2. Management of AEs: in a timely manner
3. Systematic and standardized recording and reporting of AEs: data collection to include safety data, at least all SAEs reported and assessed for causality, close coordination between national TB and PV structures

Three levels of aDSM

1. Core package: requiring monitoring for and reporting and management of all SAEs
2. Intermediate package: includes SAEs as well as AEs of special interest
3. Advanced package: includes all AEs of clinical significance

aDSM Eligibility - aDSM applies primarily to the following:[12]

1. MDR-TB and XDR-TB patients treated with new medicines, such as BDQ or DLM
2. MDR-TB and XDR-TB patients enrolled on treatment with novel regimens, including the shorter MDR-TB treatment regimen
3. All other XDR-TB patients on second-line treatment, as these regimens usually include multiple repurposed drugs

Once coverage of these patient groups is reached, aDSM can extend to other MDR-TB patients on treatment.

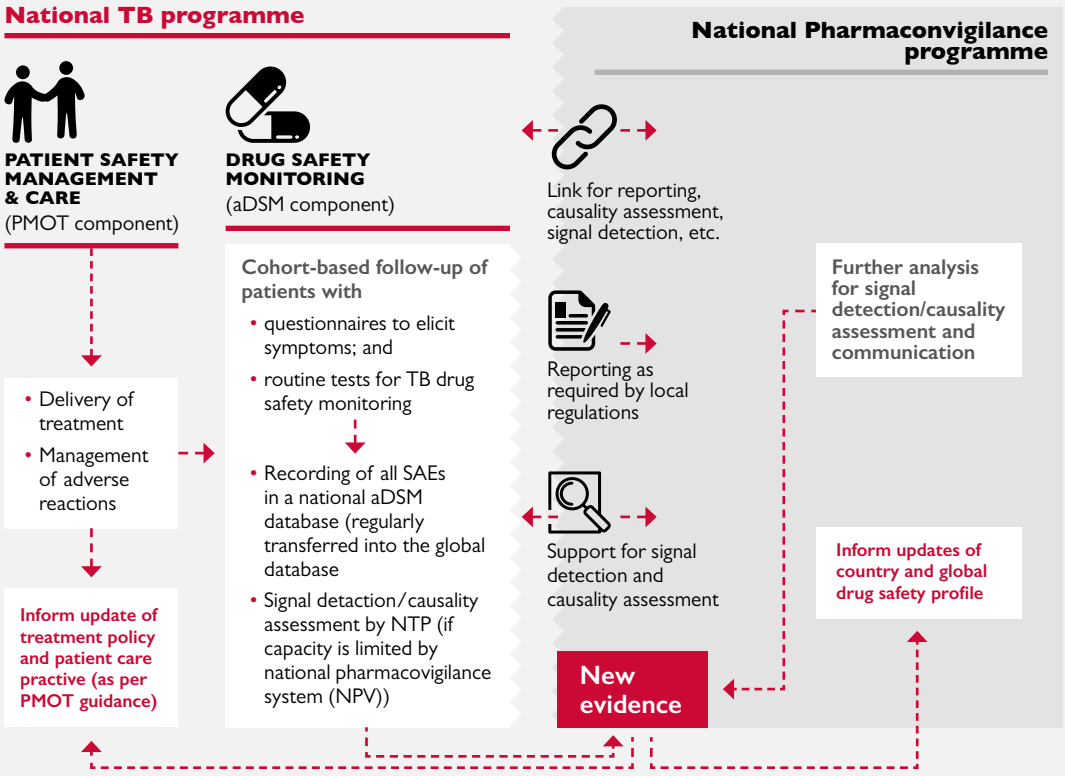
In 2016, a global aDSM database was created, coordinated by the Special Programme for Research and Training in Tropical Diseases at WHO Headquarters (TDR) and the WHO/GTB. The Luxembourg Institute of Health (LIH) is responsible for its day-to-day management. National programs and other bodies can report AEs to the database for patients treated with medicines which are new or repurposed (originally approved for an indication other than TB). Eight key steps have been identified for programs to follow when introducing aDSM.

Key steps in aDSM implementation[13]

1. Create a national coordinating mechanism for aDSM
2. Develop a plan for aDSM
3. Define management and supervision roles and responsibilities
4. Create standard data collection materials
5. Train staff for collection of data
6. Define schedules and routes for data collection and reporting
7. Consolidate aDSM data electronically
8. Develop (or use existing) capacity for signal detection and causality assessment

The WHO DR-TB treatment policy updates aim to improve the assignment of patients to treatment regimens that can increase the likelihood of cure. However, important uncertainties remain on the effectiveness and safety of the treatment options, both regarding older and newer medications. Thus, more evidence will be required and new studies will need to be undertaken to ensure that treatment is better targeted according to the patient profile. aDSM and the global aDSM database aim to document signals of previously unknown or poorly documented adverse events in patients on new drugs or novel MDR/XDR-TB regimens.[14]

Figure 4. Coordination between NTP and National pharmacovigilance system (NPV) in implementing aDSM



Source: "WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens", presented by Dennis Falzon, WHO/HQ Global TB Programme, Geneva 25 April 2017, Bangkok, Thailand.

New TB drugs for DR-TB: Overview, clinical considerations, ethical issues, informed consent for programmatic introductions

Dr. Vivian Cox and Dr. Sein Sein Thi, USAID Stop TB Partnership DR-TB Clinical Consultants, described the clinical considerations and management for DR-TB patients enrolled on treatment with ND and STR. Their presentation emphasized the uniqueness of DR-TB treatment-toxic drugs, underlying co-morbidities and polypharmacy and resulting AEs/ADRs, and discussed the clinical management of AEs/SAEs and its importance for patient outcomes. Dr. Cox and Dr. Sein Sein Thi provided background to newer drugs and global access to those drugs, including BDQ and DLM, as well as repurposed drugs such as linezolid and clofazimine. They also explained the "Triage" approach in choosing the DR-TB treatment regimen in patients with confirmed RR-TB or DR-TB, an important change in the approach to choosing a treatment regimen after the WHO approved the STR as the first regimen of choice for DR-TB (meeting specific criteria). Briefly, the STR should be the first regimen chosen for DR-TB unless patients are at risk for second line drug resistance or if they have extra-pulmonary disease, or are pregnant. If patients do not meet these criteria, they should be started on a ND regimen (bedaquiline or delamanid), which should also be used if patients fail or intolerant of the STR (see Figure 5).

Drs. Cox and Sein Sein Thi also provided an overview of publications and programmatic experience with new drugs. Finally, they outlined the ethical issues related to new TB drugs, informed consent for programmatic introductions and clinical considerations. For more detail on the power point presentation, please refer to the attached document, Day 1-Overview of New Drugs for DRTB.

What is Patient Triage?

Patient triage is the process of rapidly determining the best treatment for patients based on their specific needs and anticipated outcome of care. For tuberculosis (TB), this requires quick and accurate diagnosis of TB disease and the different patterns of anti-TB drug resistance by rapid molecular based tests. A patient can then be treated with the most appropriate drug treatment following KNCV's "Right Diagnosis, Right Treatment" principle (https://www.kncvtbc.org/en/what-we-do/the-kncv-patient-triage-concept/).

The Patient Triage concept begins with an individual presumed to have TB and ends with the patient permanently cured. Using rapid molecular based laboratory tests, an individual can have the absence or presence of TB disease confirmed. Depending on susceptibility to rifampicin, the TB patient can then be "triaged" to either a first-line or second-line drug regimen. Using rapid molecular tests for second-line drug resistance, patients with rifampicin resistance can be triaged to the most appropriate DR-TB regimen. Overarching activities, such as those required to ensure adequate and appropriate infection control measures should also be in place and are essential for a comprehensive approach.

Ethics and informed consent

Once a patient has been triaged, s/he must be made aware of the benefits and possible side effects of treatment and provide informed consent. Local practice for informed consent should be observed, whether that be written informed consent versus verbal consent following a clear description of the risks and benefits, giving patients the choice to refuse treatment with

ND or STR for DR-TB. A core package of aDSM should be in place to track and collect ADR information to better help patients and understand the effects of the drug.

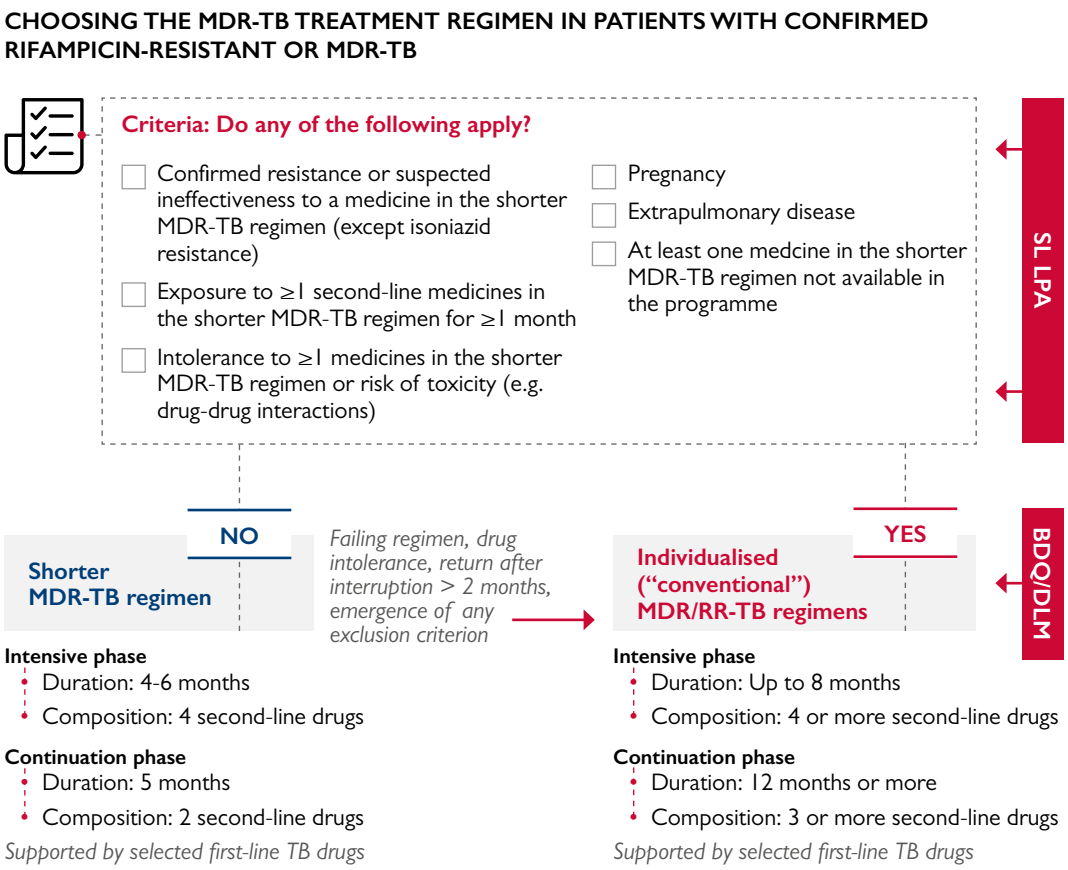
Clinical considerations

- Patient selection criteria
- Regimen composition (multiple QT prolonging drugs, drug dosing)
- Length of therapy: extension beyond 24 weeks
- Inpatient or outpatient initiation
- Combination of BDQ and DLM
- Special populations – children, pregnant women, HIV positive patients

Other considerations

- New drugs are no longer new – safe, less toxic, and effective
- Use with minimal modifications to current PMDT clinical programs and as part of effective combination therapy
- Patients with resistance or intolerance to SLDs should be prioritized
- Most data are for patients 18-65 with pulmonary disease, but can be used safely in other populations
- Plans for rollout of new drugs at the country level are an essential component of improving DR outcomes

Figure 5. Triage Approach



SECTION 2

Essential structure of aDSM for TB care: what should it look like?

SECTION 2

Essential structure of aDSM for TB care: what should it look like?

Figure 6. Roadmap questions each country answered for each category of the roadmap.

Where are we today?

What are the identified gaps?

What activities are needed to fill the identified gaps?

By when will we be completing these activities? 2017/2018/2019

Resources

**Note: Detailed country roadmaps are presented below, in Annex 3.*

The aDSM roadmap presented

The purpose of the aDSM roadmap is to guide planned and ongoing activities for aDSM and pharmacovigilance supporting the introduction and scale-up of ND and STR. The goal is to strengthen coordination and partnership across all stakeholders and organizations to ensure that eligible patients can access ND/STR and that aDSM systems and reporting structures are established and strengthened.

During the workshop, the delegations from each of the participating countries were asked to consider the five key components of the aDSM roadmap (adapted from the WHO aDSM framework):

1. *National Coordination, Policy Guidelines and Implementation Plan Development* – Create a national coordinating mechanism for aDSM, develop a plan for aDSM, and define management and supervision roles and responsibilities
2. *Recording and Reporting Structure* – Create standard data collection materials, train staff for collection of data, and define schedules and routes for data collection and reporting
3. *Health Care Workers Capacity Development* – Increase staff capacity to ensure staff trainings for new drugs and novel regimens occur before patient enrollment, and to ensure that roles and responsibilities for data collection and reporting are well defined and fully supported
4. *Clinical Management* – Increase capacity of HCW and MDR-TB experts to prevent, detect, and respond to AEs/SAEs
5. *Data Management and Analysis* – Consolidate aDSM data electronically, develop (or use existing) capacity for signal detection, and enhance linkage between NDRA and NTP for data analysis and management

Designing and implementing aDSM for new drugs under programmatic conditions: Georgia Experience[15]

Dr. Nino Lomtadze, USAID/Stop TB Partnership MDR-TB Clinical Consultant and Head of Surveillance and Strategic Planning Department, National Centre for Tuberculosis and Lung Diseases (NCTLD), Georgia, presented on Georgia's experience on aDSM: how a high MDR/XDR-TB burden country operationalized the aDSM system to successfully and sustainably introduce BDQ and DLM. The presentation highlighted the key factors for success and provided lessons for other countries. For more detail on the presentation, please refer to the document, 1.Day 2-PV_Asia_Workshop_Lomtadze_Lecture 1 and 2.EDITED.ppt.

Chronology of access to New TB Drugs

- **2013** Start BDQ Compassionate Use (CU) Program
- **2014** MSF supported scale up of CU and programmatic use of BDQ and CU of DLM
- **Aug. 2015** Programmatic use of BDQ through USAID Donation Program
- **Nov. 2015** Universal access to diagnosis/treatment for TB including "pre-XDR" and XDR-TB. Also, updated national TB guidelines, endorsed by the Ministry of Health, included MDR/XDR-TB treatment regimens and new drug safety monitoring schedule consistent with WHO guidance

Chronology of practical steps taken

- **2014** National BDQ implementation plan developed with the USAID project, approved by the National TB Council that is chaired by the Minister of Health
- **Jan. 2015** Technical Working Group created to coordinate new drug implementation, including PV, led by National Center for Tuberculosis and Lung Diseases, Georgia (NCTLD)
- **Mar. 2015** Ministry of Health-approved new voucher funding for safety monitoring linked with new drug use
- **Apr. 2015** Georgia became a primary candidate to receive BDQ through the USAID BDQ donation program, and the BDQ handover was conducted in October 2015
- **Jul. 2015** Mobile Consilium was launched by the NCTLD with the support of the Global Fund TB Program

As of 31 March 2017, a total of 361 patients have been enrolled on ND, of which 262 patients are on BDQ (20 patients through CU and 242 through programmatic use), and 99 patients are on DLM (12 patients through CU and 87 patients through programmatic use). As of end April 2017, a total of 211 patients remain on treatment.

Before 2014, Georgia was PV "naïve" for all diseases, including TB. With the support of MSF, the country received training on XDR-TB treatment in May-July 2014, with a focus on the monitoring and management of AEs and the reporting of SAEs, with data entered into an MSF clinical database. Technical assistance to establish a PV system was provided in May 2015 through System for Improved Access to Pharmaceuticals and Services (SIAPS) and the USAID BDQ Donation Program. Over a three month period, a comprehensive system was developed by SIAPS experts in collaboration with the NCTLD and MOH to report baseline and monthly AE of clinical importance; however, this system was ultimately not implemented. In August 2015, a training of trainers was conducted on clinical management of AEs in line with severity grading, with SIAPS technical assistance. This training launched PV implementation for Georgia.

Following the initial implementation, the Georgia NTP, SIAPS, University Research Company (URC) and MSF met in September 2015 to establish a new framework for the introduction of aDSM for new anti-TB drugs, as per WHO recommendations.

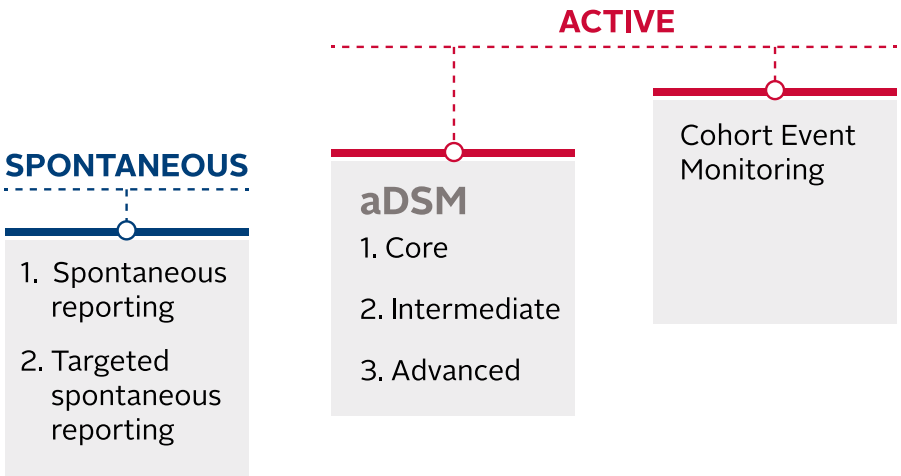
The decision was made to implement the core aDSM package, the most basic of the three levels of aDSM, which requires monitoring and reporting of all serious AEs. The core aDSM package should be applied to all drug-resistant TB patients on treatment as part of routine programmatic practice. In addition, sentinel sites participating in the MSF endTB project should implement the intermediate and advanced aDSM packages, which include AEs of special interest and of clinical significance, expanding beyond serious AEs alone. Georgia also established a transition plan from the core to the intermediate and advanced packages, which will be led by the NTP in anticipation of the endTB Project's completion.

From October 2015 through June 2016, further training was conducted to facilitate broad implementation of the Ministerial Decree requiring mandatory SAE recording and reporting (core aDSM), which was issued in June 2015. This Ministerial Decree represents very high level support within the government for aDSM, which likely represents one of the key reasons for the country's success on aDSM. Training materials and lectures for TB doctors and programmatic staff were developed by partner agencies, and more than 200 TB doctors and PMDT staff were trained on aDSM.

Designing ADR/SAE reporting structure from patient level to local NDRA and to global level

Dr. Anh Innes, FHI 360 Chief of Party, Control and Prevention of Tuberculosis Project, and Clinical Assistant Professor of Medicine (Adjunct), University of California San Francisco, explained how countries at different levels of aDSM/PV capacity can design reporting forms, standard operating procedures (SOPs), and guidelines, how their existing reporting structures can serve the needs of TB programs, and how collected data flow to and between NDRAs and NTPs.

Figure 7. Spectrum of pharmacovigilance



Determining the level of aDSM is a critical step that influences the design of the data collection system that should be in place for effective implementation. Namely, the core, intermediate and advanced levels of aDSM determine the type of AEs recorded and reported, as summarized below.

Serious: reported for core aDSM and are AEs that lead to

- Death
- Hospitalization or prolongation of hospitalization
- Life-threatening
- Permanent disability
- Birth defect or congenital anomaly
- Events that do not result immediately in one of these outcomes but that require an intervention to prevent the above from happening

Special Interest: reported for intermediate and advanced aDSM and were documented during clinical trial and of interest to report, independent of seriousness, severity, or causality.

- Peripheral neuropathy (paresthesia)
- Psychiatric disorders and central nervous system toxicity
- Optic nerve disorder (optic neuritis) or retinopathy
- Ototoxicity
- Myelosuppression
- Prolonged QT interval
- Lactic acidosis
- Hepatitis
- Hypothyroidism
- Hypokalemia
- Pancreatitis
- Phospholipidosis
- Acute kidney injury (acute renal failure)

Clinical Significance: reported for advanced aDSM, and are AEs that are

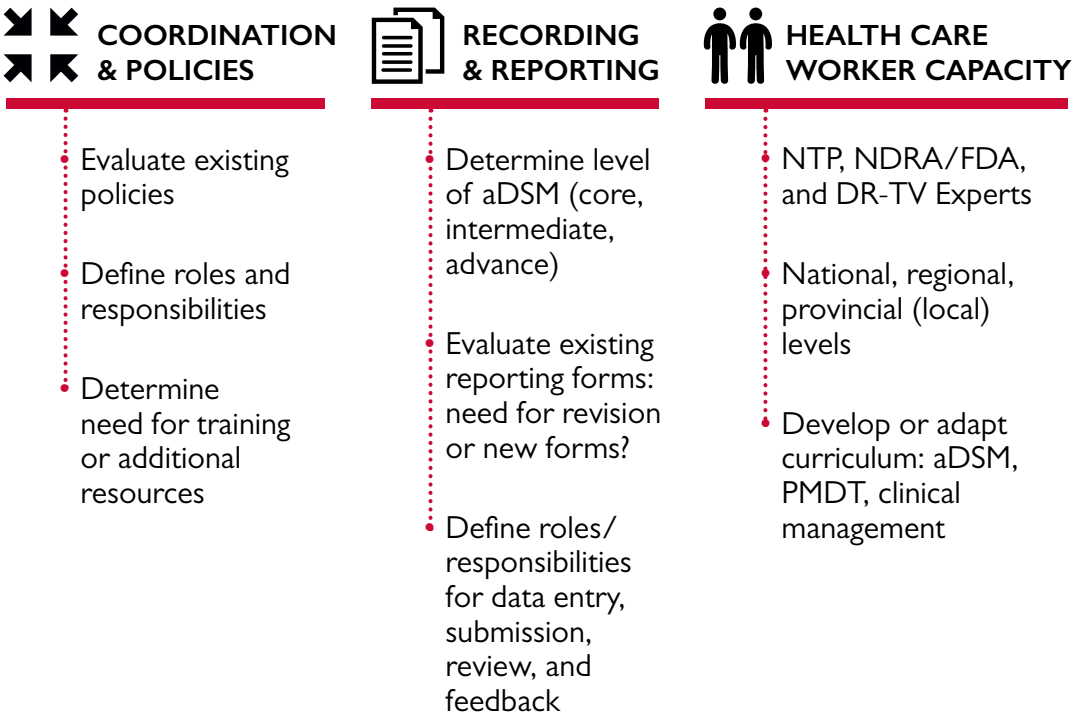
- Serious
- Of special interest
- Leads to discontinuation or change in drug dosage or treatment
- Is judged as otherwise clinically significant by the clinician, even if not listed as "special interest"

Once the level of aDSM has been determined, the next step is to evaluate the existing, routine DR-TB data collection forms to decide whether new forms must be created for aDSM or whether the existing forms can be revised. Three types of "events" or visits are captured for aDSM: treatment initiation; monthly (routine) visits; and adverse events. A key consideration for sustainability is the human resource capacity, both at the site level to enter data as well as at the national level to review the data. These considerations are critical for sustainability.

Finally, technical capacity must be built among key stakeholders, whose participation and coordination are necessary to ensure aDSM implementation. These stakeholders comprise three main categories: National TB Program (public health) officers; National Drug Regulatory Authority (pharmacovigilance centers); and DR-TB experts, who are often clinical or academic. aDSM trainings should include all three categories if possible, at both the national and decentralized (regional or provincial) levels, depending upon the country's health system structure. aDSM and PMDT training curricula have been developed by multiple technical organizations and projects and can be accessed and adapted to the country setting for these trainings.

National level cohort monitoring and case-based trainings should also be conducted to build capacity on ND and STR treatment and aDSM, and ideally should include NTP, NDRA, and DR-TB experts. Since many sites in most countries may have small cohorts, each individual physician or public health professional may only have exposure to a small number of patients. Thus, one primary goal for these cohort reviews is to increase exposure to clinical dilemmas and decisions, so that sites can learn from each other, and to identify potential, addressable issues that are identified in the routine cohort reviews. For example, a routine review may reveal that very low body weight patients may have more adverse events with a new drug; these trends can then be further followed up to determine if regimens should be adjusted or if other actions are required.

Figure 8. aDSM Roadmap



Source: "Designing an ADR/SAE system: from the patient to national and global levels", Dr. Anh Innes, FHI 360 Chief of Party, Control and Prevention of Tuberculosis Project, Clinical Assistant Professor of Medicine (Adjunct), University of California San Francisco, 26 April 2017, Bangkok, Thailand.

Management of SAE data and causality analysis

Causality Assessment (CA) provides a structured approach to assessing the relationship between a drug(s) and an adverse event and is conducted in order to assess the degree to which a reported event is causally associated with the suspected drug(s). CA is a measure of the likelihood that the drug was responsible for causing the event,[16] and differentiates between adverse events and adverse drug reactions, the former describing events that occur during treatment with a drug(s) but is not necessarily related to the drug; and the latter describing events that occur during treatment with a drug(s), which has been deemed responsible for the event.

There are many algorithms that have been used to conduct CA; the two most commonly used methods are the WHO-Uppsala Monitoring Center (UMC) algorithm and the Naranjo algorithm. The WHO-UMC Causality Categories evaluate whether the event parameters (reasonable time relationship to drug exposure; no other explanation such as drugs or disease; event is definitive i.e. specific problem; positive de-challenge; positive re-challenge) are certain, probable, possible, unlikely, unclassified, or un-assessable. The Naranjo algorithm uses a series of 10 questions that can be answered "Yes", "No", or "Do not know" and are weighted with scores ranging from -1 to +2, with the score ranked as a probability scale. It should be noted that CA often have ow inter-observer reliability and that assessors using either of these two algorithms may draw different conclusions based on the same information.

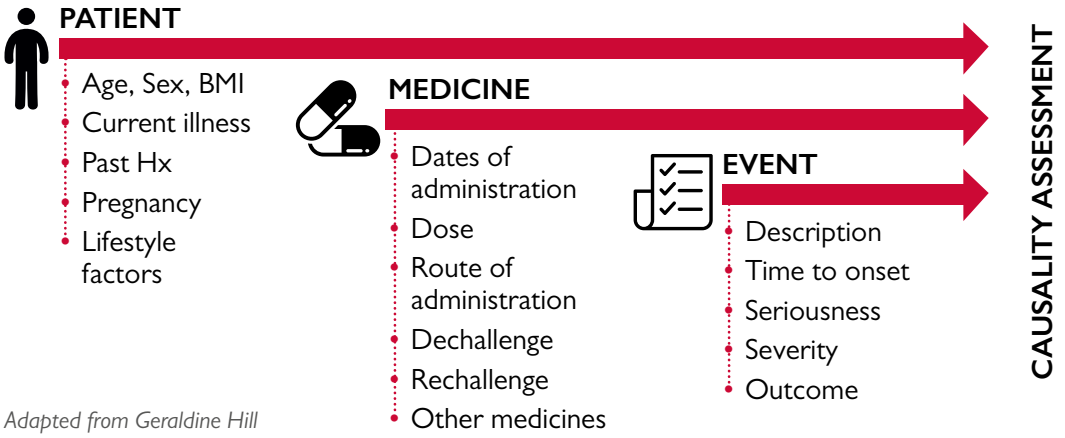
A critical element to improve the accuracy of these assessments is the amount and quality of available data. The availability and quality of data therefore requires strong participation and engagement of the hospital site, which in many cases may be the treating physician and their team. CA are therefore time intensive, requiring comprehensive data to enable the fullest picture of the patient, the medicine, and the event (Figure 8) in order to maximize the accuracy of the CA. For countries or settings with limited resources or capacity, it may be decided to limit CA to only serious AEs in order to avoid overloading the health system. In the ideal setting, CA are conducted by individuals within a national pharmacovigilance center, with review of the cumulative cases on a regular basis (quarterly or semi-annually) to identify trends or necessary actions. In most settings, however, in which aDSM and CA capacity may be new or limited, the assessment may be more accurate if conducted at the site level in order to maximize the amount and quality of available data. Questions can be asked to help discern these details:

1. Who should conduct the assessment?[17] i.e. who determines whether the event was related to the drug/regimen?
   - **Site level:** data easily available, can be done quickly
   - **National level:** less subjectivity, likely delayed since national level consilia normally involve national level experts

2. At the national level, is there a "Causality Assessment Committee" that evaluates CA reports (quarterly, semi-annually)? If so, the following experts should be included:
   - DR-TB expert, clinical specialists ("on call" depending on specific cases), pharmacologist, toxicologist

Multiple data variables are required to accurately determine causality: the more data the better.

Figure 9. Variables required to determine causality



Adapted from Geraldine Hill

Source: "Causality Assessment: Prep for Group Work", presentation by Dr. Anh Innes, FHI 360 Chief of Party, Control and Prevention of Tuberculosis Project, Clinical Assistant Professor of Medicine (Adjunct), University of California San Francisco (adapted from Geraldine Hill, Interregional PV Training, 3-5 March, Denmark, 2014), 26 April 2017, Bangkok, Thailand.

How to properly conduct CA training[18]

- Choose trainees (Who should be trained?)
  - Level: national vs. local/provincial
  - DR-TB experts, NTP
  - Academic faculty: medicine and pharmacy (Causality Assessment Committee)
- Choose algorithm
  - WHO-UMC
  - Naranjo
- Develop a training strategy to ensure a standard framework and approach, not necessarily to ensure the "right answers"
  - Known subjectivity: low inter-observer reliability (different observers)
  - Assessment may also change over time (same observer with more data that may become available over time)

SECTION 3

Moving forward with urgency: aDSM implementation at country level

SECTION 3

Moving forward with urgency: aDSM implementation at country level

Principles in the management of adverse events[19]

- Early identification (treatment monitoring): treat immediately and adequately
- Rule out other cause/ comorbidity and correct underlying cause
- Consider additive or potentiating SE* with concomitant therapy
- Consider drug-drug interaction (e.g. CYP3A4 inhibiter– ketoconazole, LPV/r)
- Some adverse effects may disappear or diminish over time; encourage to tolerate with psychosocial support
- Mild to moderate AEs: use ancillary drugs to alleviate symptoms
- Permanent dose reduction (not applicable for BDQ/ DLM) or definitive stopping, as a last resort

Management of new drug toxicities as a part of good clinical care

The clinical management of ND/STR toxicities is a critical component of aDSM and contributes to the overall DR-TB patient's successful treatment outcomes.

Dr. Sein Sein Thi and Dr. Vivian Cox provided an overview of the management of clinical toxicities due to ND/STR, the role of diagnostics and lab/clinical monitoring as part of routine care, an approach to managing drug toxicities by severity grading, and discussed issues and recommended solutions. They also provided real life case studies of common occurring toxicities and how those cases are managed and reported.

Roadmap: from pilot project or research to country-wide implementation

The presentation by Dr. Edine Tiemersma, a senior epidemiologist at KNCV Tuberculosis Foundation, laid the groundwork for the development of the country plans to implement aDSM. The presentation also highlighted principles to consider when planning next steps, timelines and responsibilities for partners and stakeholders and to help countries identify any technical assistance needs.

Scaling up aDSM from pilot project to the national level – Tajikistan and Indonesia examples

TAJIKISTAN The aDSM intermediate package was implemented for all MDR-TB and XDR-TB patients on new drugs at three pilot sites. To integrate recording and reporting, data for all AEs of clinical significance were

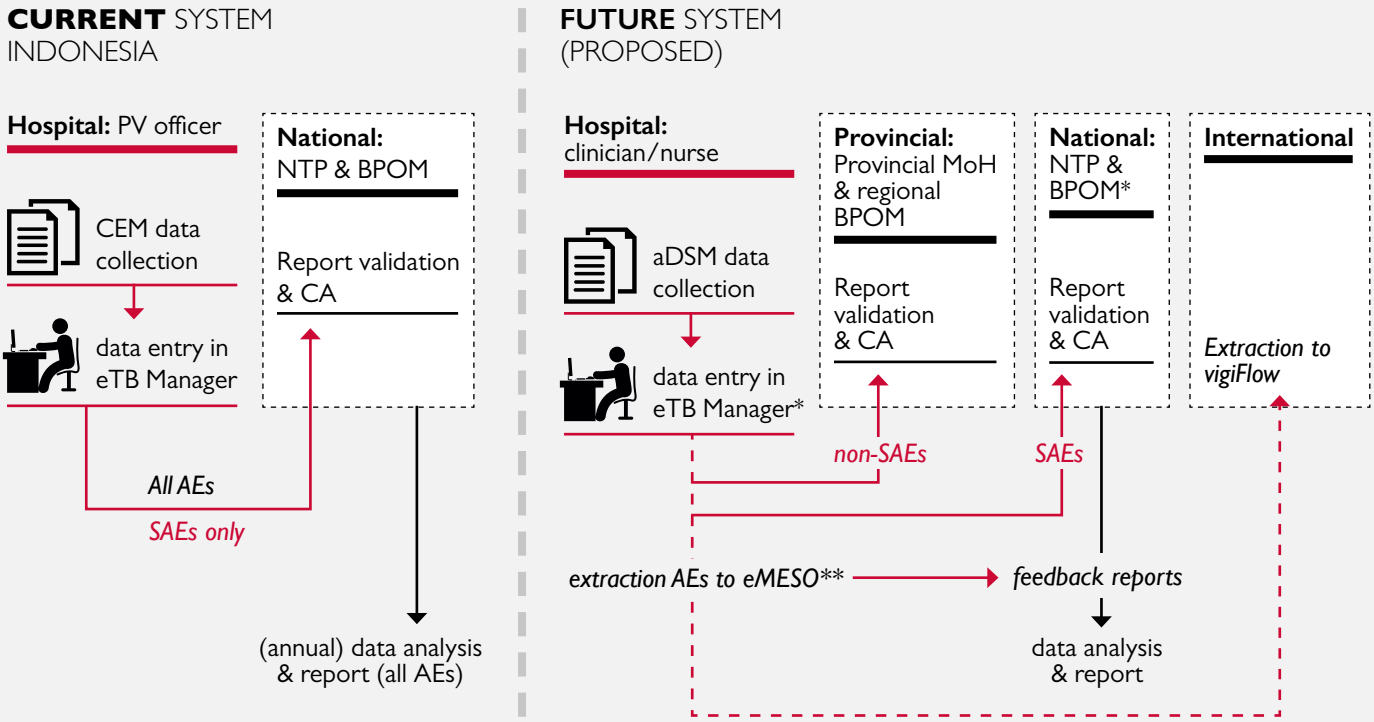
* Note: Detailed information on issues and recommended solutions for SE management are presented in Annex 2 and the *full power point presentation*, Day 3, Management of NDT Toxicities _Sein-Vivian.

registered on paper forms in the patients' files, as no electronic data collection has thus far been undertaken (however, data can be collected via a desktop application on personal computers, but the system is not internet based). Data for AEs of special interest and SAEs are also entered in the Patient Triage Application (PTA). Data are then validated and automatically exported to Excel and PDF files so that system reports can be generated and open for customization and integration into national surveillance systems.

INDONESIA Cohort Event Monitoring has been used for 100 patients on BDQ in three pilot sites in different parts of the country. There are plans to implement patient triaging and STR nationwide to approximately 8,000 MDR-TB patients, expected in 2017. However, the CEM data collected by the PV officer only include SAEs and not all AEs. The data are then reported to the national NTP & NDRA (BPOM).

Recording and reporting (R&R) data forms for CEM in Indonesia were developed by the PMDT group of NTP with guidance from KNCV, in collaboration with the BPOM. The three forms include a baseline treatment initiation form, a treatment monitoring form and a laboratory test result form.

Figure 10. Scaling up from pilot project or research to country-wide implementation in Indonesia – current and future system (proposed)



Source: "Roadmap: from pilot project or research to country-wide implementation", presented by Dr. Edine Tiemersma, KNCV Tuberculosis Foundation, 27 April 2017, Bangkok, Thailand.

**BPOM: the Indonesian National agency of Drug and Food Control*
***eMESO: an electronic reporting system*

Figure 11. Scaling up aDSM: Challenges and potential solutions[20]

Challenge	Potential solution
Recording and reporting (R&R) is time consuming	Keep R&R to a minimum while ensuring that enough data is collected for proper CA; only enter aDSM data in the package chosen; avoid duplicate R&R
Digital data collection/entry	Ideally, data entry should be conducted at the site; Internet-based systems should also have an offline mode for quick and safe entry of data
Weak capacity of national PV centers because of understaffing and high turnover, irregular CA for all reported AEs, no data validation, and no feedback reports	Further international awareness raising and advocacy needed to increase funding for PV centers.

Source: _ presented by Dr. Edine Tiemersma, KNCV Tuberculosis Foundation, 27 April 2017, Bangkok, Thailand.

Figure 12.An Overview of CEM vs aDSM

	CEM	aDSM
Description	Prospective cohort study	Prospective systematic (programmatic) data collection
Main purpose	Early warning system	Strengthen management & monitoring of AEs
When used	Used in early post-marketing	Used for M/XDR-TB patients
# patients included	Limited and pre-defined	Not pre-defined
Duration	Until defined #patients have complete FU	Not pre-defined
Follow-up	For a duration appropriate for drug(s) under study	At least for full duration of treatment (and if possible beyond)
Denominator	All patients enrolled in cohort	As CEM
Type of AEs collected	Any AE detected	Depends on package (but at least judged clinically significant)
Causality assessment	All AEs reported	May be on selection of AEs

Conclusion

The ten countries participating in this regional workshop have different health systems, health contexts, and experience, which impact the technical capacity, resource allocation, and challenges for applying and implementing the aDSM framework. However, delegations from each country were able to identify the gaps and solutions needed to take concrete actions for all stakeholders involved in implementing the aDSM roadmap and achieving international standards for pharmacovigilance.

Challenges shared by some of the countries included the lack of commitment and communication among relevant stakeholders, including the NDRAs and NTPs; the need to revise and update data collection procedures to include MDR-TB, and to integrate reporting mechanisms among agencies and from the patient level to the country level. Healthcare workers are limited in number and capacity, highlighting the need to improve the clinical management of MDR-TB. In addition, roles and responsibilities for all major stakeholders and participants in aDSM need to be established, given the distinct role required of public health professionals (NTP), drug regulatory authorities (NDRAs), and DR-TB experts. Finally, countries need to register new drugs, such as BDQ, before the BDQ Donation Program ends in order to ensure that there is no interruption in the drug supply.

Moving forward with implementing the aDSM framework requires sustained effort and commitment. This workshop prepared participants to develop comprehensive aDSM plans that can be efficiently and effectively implemented and scaled up to the national level. Common barriers to aDSM implementation were highlighted and included concerns on managing suspected and confirmed toxicities for ND/STR; as well as human and financial resources to maintain aDSM and ensure quality care to handle ADRs. Targeted training packages and technical assistance were requested from all countries to implement the aDSM framework, and to maximize treatment of all eligible DR-TB patients with ND and STR. The need for training and technical assistance will increase in the near term, given the WHO's endorsement of the STR as the first regimen of choice for MDR-TB (if eligible by drug susceptibility profile) as well as the expectation for more ND in the pipeline for TB. From the discussions and planning that resulted from the workshop, countries will be able to make progress in developing pharmacovigilance systems that will increase the quality of care and treatment options for DR-TB patients.

ANNEX I

Reference for SE management: issues and recommended solutions

ANNEX 1

Reference for SE management: issues and recommended solutions[21]

Area	Specific gaps	Potential/Recommended Solution
Lab/ diagnostic	• No availability of LPA • No availability of 2nd line DST • Loss to follow-up (LTFU) between GeneXpert and Line Probe Assay (LPA) • Transport • Early tracking of eligible patients	• Equip – 1st option • Refer to nearest center: • In-country/out-country referral to an accredited lab • Decision by lab to forward/proceed for LPA testing from the same sample set • Motorbike/public transport/out sourcing/ courier service • Alerting system, a dedicated person to track in the team
Clinical monitoring	• No ECG at PMDT sites • QTc/basic electrocardiogram (ECG) interpretation • Maintenance/accuracy of result • Biochemistry testing • (esp. K+,Mg+,Ca+) • No machine on site • Timely availability • Accuracy of result • Abnormal value • No test available for Mg+ at PMDT sites • Audiometry • No machine on site • Testing technique/variation of results/interpretation • Maintenance • Vision test vs availability of ophthalmologist	• Equip – 1st option • Refer to nearest center • Train staff • Refer in case of doubt (m-health system – whatsapps/e-mail) • Clinically concern: timely referral to hospital with critical care unit (CCU)/ intensive care unit (ICU) for specialist care • 6 monthly calibration/service agreement with supplier • Equip – 1st option • Refer to nearest center (reliable lab with proper QA system) • Ensure to get within 24 hours • Alarm system in agreement with lab for abnormal value • Proper sample collection/transport/time/ calibration • Train staff for management • IPD care for G3 patient from far distance • Mg+ supplementation to refractory hypokalemia cases • Equip – 1st option • Refer to nearest center • Proper location of machine (quiet place/ sound proof booth • Train staff • Annually/service agreement with supplier • Take clinical management decision • Ensure having Ishihara test/Snellen Chart, train staff

Area	Specific gaps	Potential/Recommended Solution
Patient's factors	• Hospitalization • Patient seeking care at other GPs/specialists for other morbidity or AEs	• No mandatory hospitalization for clinically stable or case with no risk of potentiated SE • But need an established link with a hospital for specialist care • Proper information transmission to the referral hospital • Educate patient/family about AEs/SAEs and to inform to PMDT sites • Patient card with info about new drug AEs/ SAEs (a good example from Pakistan)

Source: "Management of new drug toxicities as a part of good clinical care", presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 27 April 2017, Bangkok, Thailand (taken from endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs, Version 3.3. http;//endtb.org/resources/endtb-clinical-guide-v33.

ANNEX 2

Status of implementing PV/ aDSM for MDR-TB for each country

ANNEX 2

Status of implementing PV/aDSM for DR-TB for each country

BURMA/MYANMAR

Status of implementing aDSM for MDR-TB

Launched the New Drugs endTB program in March 2016 in a collaboration between NTP and MSF-HQ

- Enrolment criteria: pre-XDR-TB, MDR-TB failures and MDR-TB patients who cannot tolerate standardized regimen
- Based on Second Line DST Results (NTRL and Antwerp)
- Regimen constructed in consultation with Expert DR-TB committee as per history and resistant patterns
- Total of 19 patients enrolled, 14 patients ongoing treatment (4 –died, 1 –LTF)
- (7 patients with BDQ, 7 patients with DLM)
- 10 SAE encountered and reported
- STR pilot program to begin in June 2017, for 200 patients
- Procurement process for drugs and lab materials for second line LPA and first line DST

Status of country PV system

- No official PV center in FDA
- Have AE/ADR spontaneous monitoring system
- ADR forms are developed and distributed to the Drug Advisory Committee, medical associations, private hospitals and teaching hospitals, and are available on the drug safety network – mobile application for Android and iOS users
- Active reporting of serious SAEs by the endTB project using 3 forms: one in the local language (submitted to the FDA), one on SAEs using the MSF Form (submitted to MSF-HQ), and one NTP form submitted to the NTP manager, and then to the FDA director
- Reporting system through post and email
- Computerized data entry system; database updated by staff in the central FDA each time it receives an AE form. Director analyzes the data but no written report is produced

PV system challenges

- Lack stable funding
- Lack PV policies and guidelines
- Limited human resources for data collection, reporting and analysis
- Limited technical support to PV staff

NTP and FDA collaboration

- National aDSM implementation plan prepared and endorsed by NTP
- Core committee for aDSM includes the director of the FDA Drug Control Section, clinical professors, NTP national program manager, TB specialist hospitals (MSF Holland and WHO as partners)

Next steps for PV system

- With the support from Challenge TB project, NTP plans to develop a national SOP on aDSM in close collaboration with FDA
- First aDSM consultation workshop conducted in March 2017, with KNCV support
- After SOP finalization, plan for TOT, including causality assessment
- In the longer term, plans to implement electronic data management system, and for FDA to consider possible membership in WHO International Drug Monitoring through Uppsala Monitoring Center for PV strengthening

CHINA

Status of implementing aDSM for MDR-TB
- BDQ approved by CFDA in Nov. 2016 and BDQ is being acquired via USAID-Janssen donation program
- Plan for enrollment of 1,000 patients at 15 sites in 2017-2018
- DLM not yet approved by CFDA and is thus not accessible
- STR is not yet in NTP but is being evaluated
- CFDA AE reporting and TB electronic reporting system in place

Status of country PV system
- PV database managed by Clinical Center on TB (CCTB/NTP)
- Data reported by hospitals to CCTB, when then analyzes the data and reports to GDF, Janssen (China), CFDA, and MOH
- CA data reported from pilot site to CCTB

PV system challenges
- Limited experience of aDSM practices for TB staff at each site
- Targeted trainings are needed
- AE management protocols not fully developed and AE safety committee and work standards not established
- Human resources at central and site levels are limited, and thus timely and accurate reporting remains a challenge

NTP and FDA collaboration
- Routine mechanism between NTP and FDA not established and roles not clearly defined

Next steps for PV system
- Develop PV database, establish coordination mechanism between NTP and CFDA, and establish safety committee in Q2 2017
- PV/aDSM R&R training and pilot implementation conducted in Q3 and Q4 2017
- Scale-up of PV/aDSM in 2018-2019

INDIA

Status of implementing aDSM for MDR-TB
- Six initial sites identified for BDQ-CAP and CEM in place for these sites
- More than 400 patients currently on BDQ regimen
- aDSM still a new concept for disease control program
- PV program monitors only AE/ADR and
- AE/ADR reporting integrated in latest guidelines for PMDT management
- Newer drugs such as BDQ and introduction of STR for MDR-TB under consideration
- Web-based Nikshay to monitor TB patients and integrate R&R

Status of country PV system
- 202 AE monitoring centers (AMC) linked to Revised National TB Control Program (RNTCP) facilities for ADR reporting, which is conducted monthly
- Suspected ADR reporting format used for AE/ADR reporting
- 17 DRTB centers linked to AE monitoring centers

PV system challenges
- Timely updates of CEM treatment initiation and review forms
- Timely updates on Nikshay portal
- Monitoring district and nodal DRTB centers for ND/STR

NTP and FDA collaboration
- Formal agreement has been established between the NTP and pharmacovigilance programme of India (PVPI)

Next steps for PV system
- Strengthen PV activities related to training of field staff, linking AMCs to PHIs, and managing AE/ADRs
- R&R for AE/SAE
- Implement aDSM
- Strengthen supervision and monitoring of district and nodal DRTB centers for ND/STR

INDONESIA

Status of implementing aDSM for MDR-TB

- 65 patients enrolled in BDQ treatment (BDQ not registered)
- STR and DLM under preparation – plan to start July 2017
- No aDSM framework

Status of country PV system

- Mandatory spontaneous reporting for pharmaceutical industry and marketing authorization holders to perform PV and report data, via paper CIOMS form, to National Agency of Food and Drug Control (NADFC)
- For HCW, voluntary spontaneous reporting of PV data to NADFC
- The collecting and reporting of CEM data for BDQ: PV officer records all AEs in standard paper form and inputs data into e-TB Manager software; monitoring and evaluation undertaken at central level and issues CA
- Validation of side-effect data reported to database and then to WHO-UMC
- Risk management process: advisory committee for ADRs and other experts file causality evaluation data for ADR reports

PV system challenges

- Limited human resources for PV in hospitals and healthcare facilities, for evaluating non-serious ICSR, and for IT programmer as well as high staff turnover
- ADR report information often incomplete and lack of standardized use of terminology
- eTB Manager and eMESO software not integrated
- PV system not centralized and is not used nationwide

NTP and FDA collaboration

- NTP and NADFC have developed PV for TB drugs
- NTP and NADFC have implemented CEM for BDQ in seven hospitals
- Conduct CA for BDQ patients and serious ADR
- NADFC strengthen PV and NTP to develop aDSM; collaboration to develop PV/aDSM guideline and ADR forms

Next steps for PV system

- Strengthen PV system and develop regional PV center
- Enhance collaboration and coordination between NTP and NADFC
- Discuss feasibility of and next steps for implementing aDSM for TB drugs
- Encourage NTP to ensure that all TB drugs are registered

PAKISTAN

Status of implementing aDSM for MDR-TB

- Total of 116 patients enrolled on BDQ, 16 on DLM; BDQ provided since Oct. 2016
- BDQ not registered but made available on special "NOC" from the Drug Regulatory Authority of Pakistan (DRAP)
- Patients will be enrolled on STR by Sept. 2017
- National PV committee includes physicians and pharmacists from PMDT at site level, provincial MDR-TB coordinator and pharmacist, and MDR-TB technical advisor, focal person for new drugs, NRL in charge, MDR unit data coordinator and pharmacist from the federal/central level
- Each adverse event is recorded in DRTB PV form
- SAEs immediately reported to PMDT focal person/HoD of Pulmonology Department
- For any life-threatening event, immediate clinical care provided
- Events are reported immediately to provincial committee and federal level
- Provincial and federal teams coordinate with PMDT treatment site team to ensure reporting flow is undertaken
- Federal team further reports these events to the USAID/WHO/GDF or as required

Status of country PV system

- DRAP is an autonomous body under the administrative control of Ministry of National Health Services Regulation & Coordination (NHSR & C) and is comprised of 13 divisions, with PV Centre under Division of Pharmacy Services of DRAP
  - Pakistan is an associate member of the WHO Program for international drug monitoring
  - ADR/AE are collected mainly from Market Authorization Holder (MAH)/Registration Holder (multinational pharmaceuticals) with established PV system
  - Collect ADR reports from the health care professionals and report to DRAP
  - Enhanced reporting and analysis of newly registered drugs and reporting during the post-marketing surveillance safety and efficacy studies performed voluntarily by the MAH
  - SAE reporting during the clinical trials of new drugs
  - Periodic Safety Reports voluntarily submitted by the MAH for new drugs or when requested by DRAP
  - Healthcare professional as spontaneous reporting from private tertiary care hospital (e.g. AKUH, SKMT)
- PV reporting conducted via paper ADR form available on DRAP website and can be submitted to DRAP by email; no electronic reporting of ICSR
- ADR collected and analyzed

PV system challenges

- Lack of awareness of PV and ADR reporting
- Lack of spontaneous reporting since it is not required
- Lack of human resources at national PV center

NTP and FDA collaboration

- NTP providing treatment to DRTB patients since 2010
- PV reported on monthly basis in the Electronic Nominal Registration System and analyzed by the provincial and national TB programs

Next steps for PV system

- PV regulations being developed by DRAP
- Strengthen linkages between NTP and provincial TB control programs (PTP), and NTP and DRAP
- Establish a task force consisting of members from NTP, PTPs and DRAP to implement aDSM
- Develop standardized SAE form and to integrate clinical and laboratory test records at treatment initiation, and conduct regular monthly reviews of the MDR-TB patients' treatment cards and to make it mandatory for patients on new drugs
- Sensitize healthcare workers to MDR-TB, aDSM for new drugs and reporting of SAEs

PAPUA NEW GUINEA

Status of implementing aDSM for MDR-TB

- Total of 35 patients enrolled on BDQ and 26 on STR, none on DLM
- Medicine and Cosmetic Act 1999 being revised to include PV
- SAE/ADR reporting not yet implemented
- PNG is an Associate Member of WHO-UMC
- aDSM trainings conducted in collaboration with NTP and NDOH Pharmaceutical Standards Services Branch (PSSB) for provincial TB physicians
- aDSM a key component of MTC/PV provincial roll out
- aDSM SOP integrated into PMDT SOP
- Reporting algorithm defined and piloted

Status of country PV system

- National Department of Health (NDOH) will liaise with Medicines Therapeutic Committee (MTC) from provinces, hospitals and PHAs to monitor AE/ADR and report recommendations for appropriate action, as per the PNG National Medicines Policy 2014
- MTC conducts PV activities through monitoring and reporting ADRs and conducts management of medicines procurement

PV system challenges

- SAE/ADR reporting algorithm to be implemented for core aDSM
- Need to streamline reporting process to ensure receipt at national level and reporting at global level
- NDOH needs to obtain full-member status for UMC
- Need to train key stakeholders for CA
- National ADR committee needs to be established
- Capacity building for SAE/ADR reporting
- Enhance collaboration between NTP and PSSB

NTP and FDA collaboration

- Hospital sites report to provincial PMDT/aDSM core group and then to national PMDT/aDSM core group and to NTP, as well as to provincial health authority and MTC which then report to NDOH
- NTP Causality Assessment Committee exchanges information with NDOH
- NTP reports directly to GDF while NDOH reports to UMC

Next steps for PV system

- MTC/PV roll out of aDSM training in provinces (and training of trainers) in 2017 in Southern Region (mid-May), Momase Region (end May), Highlands Region (mid-July), and New Guinea Island Regions (end July)

PHILIPPINES

Status of implementing aDSM for MDR-TB

- STR implemented at 10 PMDT treatment facilities under operational research, with 328 patients enrolled (Jul 2015-Dec 2016) and 148 patients enrolled under program conditions (Jan-Mar 2017)
- Under BDQ operational research, 72 patients enrolled as of Apr 2017 at 10 PMDT treatment facilities
- Under program conditions and compassionate use, 25 patients enrolled for BDQ and 1 for DLM as of Apr 2017

Status of country PV system

- Under operational research, reporting of all SAE (within 48 hours) and other AEs (on monthly and quarterly basis) from study sites to research team and then to central level FDA, NTP and oversight committee
- Under program conditions, all SAEs reported from PMDT facilities to NTP and FDA
- R&R on paper-based forms and is mandatory for all AEs and SAEs, with submissions to FDA via paper, electronic file (available at central level) and e2b XML file
- FDA responsible for signal detection, CA, analysis and feedback
- Data cleaning, verification and consolidation by research team

PV system challenges

- Lack clear understanding of aDSM
- PV functional only under Operational Research
- Inadequate system and capability of the FDA/PD/NTP to implement aDSM
- PViMS not yet fully operational
- Inactive National Drug Advisory Committee

NTP and FDA collaboration

- Standardized PV data to be collected
- Adopt electronic data collection, consolidation, and analysis
- Draft Implementing Procedures and Guidelines for PV data management at central and peripheral levels
- Deploy PV electronic tool in the DOH
- PV electronic tool interoperable with national TB information system
- Train staff on data collection by including PV and aDSM data management in the SSTR roll-out training

Next steps for PV system

- Finalize, issue, and disseminate draft guidelines as Administrative Order to cover both public and private sector
- Shift from CEM to aDSM Intermediate package for all health facilities
- Conduct aDSM training and establish and maintain collaborative mechanism
- Roll out PViMS implementation at the peripheral level
- Reconvene the National Drug Advisory Committee

THAILAND

Status of implementing PV/aDSM for MDR-TB

- BDQ enrollment: 2 pre-XDR cases and 18 XDR cases
- Local PV/aDSM guidelines for TB published in 2016
- DR-TB management guidelines in 2015
- DR-TB management system and regimen review process
- National TB strategic policy related to PV/aDSM awaiting endorsement

Status of country PV system

- PV reporting form and guidelines established
- PV center e-database via Thai FDA and paper-based data management at NTB
- Extended version of PV center electronic reporting for active PV in TB

PV system challenges

- Low rate of PV implementation
- Human resource training needs to be conducted at more sites
- Initiate pilot site for electronic reporting system
- BDQ use is under-reported
- R&R flow is unclear

NTP and FDA collaboration

- Coordination among stakeholders in PV reporting flow and guideline development Bureau of Tuberculosis (BTB)
- BTB and PV center form technical working group, and works with the TFDA steering committee for PV and clinical management
- BTB leads meeting and TFDA provides support
- First pilot TB clinics under BTB

Next steps for PV system

- Form monitoring working group for active TB monitoring
- Develop regular monitoring and signal management guidelines
- Monitor implementation performance

VIETNAM

Status of implementing PV/aDSM for MDR-TB

- No aDSM but under study for BDQ and DLM
- PMDT coverage in all provinces, guidelines updated with recent recommendations
- MTB/RIF coverage in all provinces
- Second line drugs LPA at 2 labs to cover all R+ cases in 2017
- 99 patients enrolled in BDQ individualized regimen (cohort study) and 101 patients enrolled in shorter regime (cohort study)

Status of country PV system

- PV in Pharmacy Law
- Spontaneous reporting: 9,912 ADR reports (2003-2016), about 10% of which related to TB drugs
- CEM: for MDR-TB at 9 sentinel sites (2014-2016), for XDR-TB at 3 sentinel sites (since 2015), conducted at PHPs, mainly under GF project
- Targeted spontaneous reporting only for HIV/AIDS program
- CA reporting

PV system challenges

- No SAE reporting forms
- Need to revise and combine existing R&R forms and implement electronic reporting
- Strengthen healthcare capacity for PV, NTP and MOH

NTP and FDA collaboration

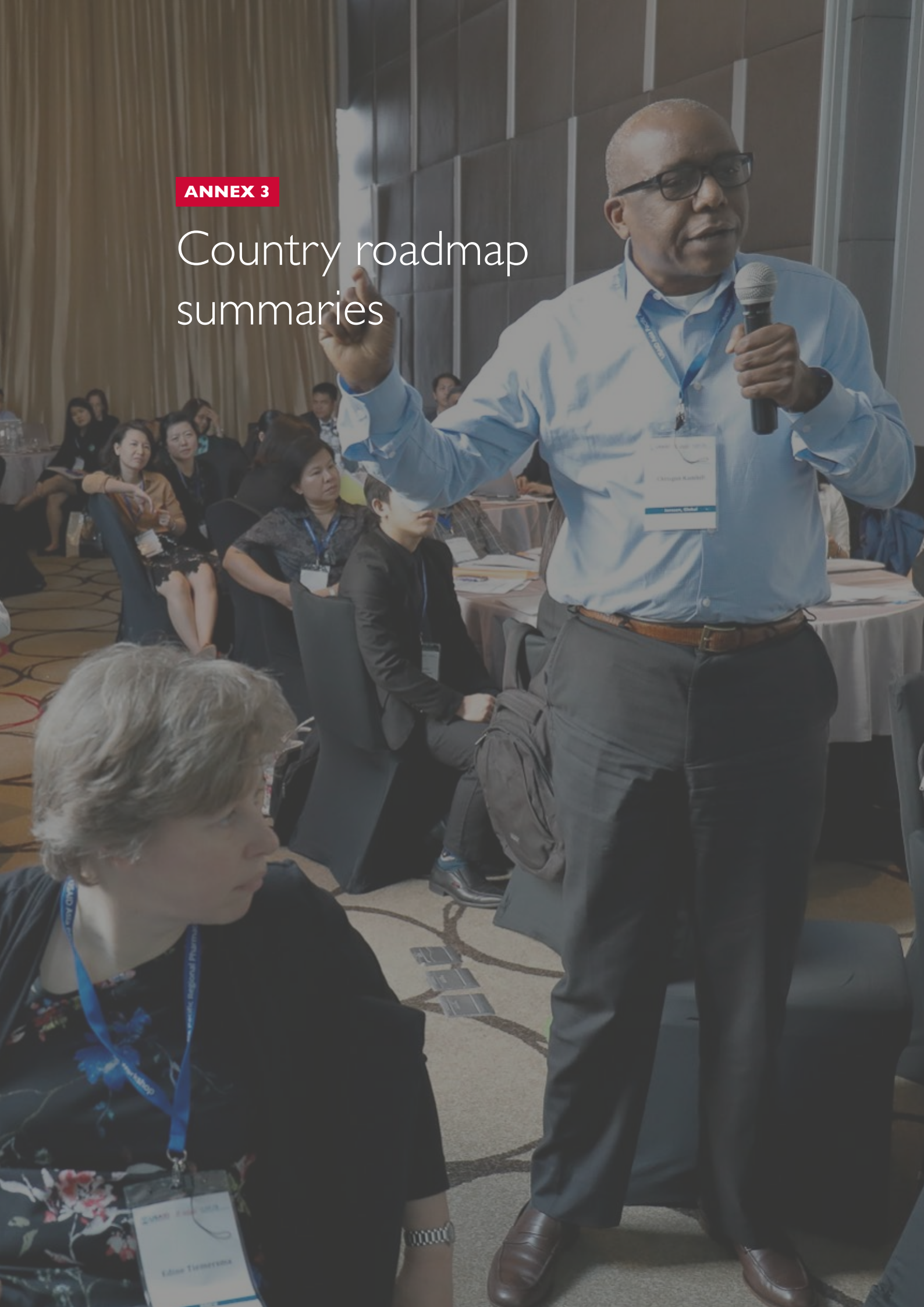
- No SOP for aDSM activities
- No defined roles for each body in aDSM activities
- No commitment to run aDSM from PV center and NTP

Next steps for PV system

- Develop a national PV system that effectively links with and supports PHP to ensure drug safety
- Establish aDSM committee and technical working group and to determine roles and responsibilities and collaboration mechanisms
- Develop SOPs and guidelines for aDSM (including revising existing forms and upgrading the electronic database) – intermediate package will be used

ANNEX 3

Country roadmap summaries



ANNEX 3

Country roadmap summaries

Coordination, Policies, Guideline, and Implementation Development

Country	aDSM Guidelines	PV Policy	Reporting type	Identified Gaps	Resources needed	Goals
Burma	National endorsed by NTP	No	N/A	Lack of strong commitment from FDA for aDSM; human resources and technical capacity; funding; technical assistance to FDA to develop comprehensive PV policy	Technical assistance (TA) and human resources (HR) support	In 2017, collaboration between NTP and FDA and HR support from international partners for capacity building for NTP and FDA staffing regarding aDSM. In 2018-2019 identify technical areas need to develop PV policy in FDA
China	In development	N/A	N/A	aDSM guideline is not well developed; routine mechanism not established between NTP and FDA; TOR of players not specified	TA for aDSM guideline development	In 2017, revise and finalize aDSM guidelines; advocate and communicate with FDA; establish coordination mechanism with FDA; discuss with key players to make consensus on TOR
India	Formal agreement has been established between the NTP and pharmacovigilance programme of India (PVPI)	New comprehensive PMDT guideline including aDSM 2017 draft ready	PVPI centers voluntarily report ADR for DS-TB	Coordination structure at national and state level between two programs is required; implementation challenges while going for country wide expansion; monitoring of all the activities	Funding from national program; support from PMDT unit at national level supported thru CTB and WHO	In 2017, coordinate aDSM activities at national and state level; implement aDSM plan with solutions and guidelines; ensure PMDT guideline includes comprehensive information on new drugs and shorter regimens. In 2018, prepare an intensified plan for monitoring of activities and expand aDSM components to PAN India

Coordination, Policies, Guideline, and Implementation Development

Country	aDSM Guidelines	PV Policy	Reporting type	Identified Gaps	Resources needed	Goals
Indonesia	No	Yes	Spontaneous for ATM drugs, use CEM for BDQ	No aDSM framework; guidelines for CEM BDQ not implemented for DR-TB PV/aDSM; BDQ not registered	NTP, NADFC, GF, partners (WHO, CTB), Pharma industry	In 2017, develop aDSM framework; revise the CEM BDQ form to include DR-TB and PV ATM guidelines; establish ministry of decree for aDSM; establish advisory committee for aDSM; follow-up on registration process of BDQ with pharma industry
Pakistan	No legislation for mandatory reporting	No	Spontaneous for PV	No legislation for mandatory reporting; absence of policies and guidelines for aDSM	TA for development of SOPs/guidelines; resources for consultation/ dissemination	In 2017 and 2018, initiate the process of legislation; adaptation of policies and guidelines
Papua New Guinea	Yes	Under revision in the medicine and cosmetics act of 1999	Duplicate reporting	No CAC; no feedback system; no standardized training package; need to capture provision for special waiver for CU, donation, CT, and off label use	Funding for consultation meeting	In 2017, have CAC as part of the PMDT committee at all levels; add TOR to national and provincial PMDT committee; create feedback system; develop standardized training package; CAC at site and national levels; PSSB with legal team and NTP work on revisions

Coordination, Policies, Guideline, and Implementation Development

Country	aDSM Guidelines	PV Policy	Reporting type	Identified Gaps	Resources needed	Goals
Philippines	Limited	Yes	Spontaneous PV	Current system no compatible for aDSM reporting of BDQ and SR drugs; PV only functional under OR; lack defined roles and responsibilities	Funding; TA	By the end of 2017, review current PV policies and draft ones for aDSM; have consultative meeting with FDA, NTP, PD, and stakeholders; finalize aDSM policies, guidelines, and implementation plans; reactivate NDAC, ensure full operation of NVPCPHP
South Korea	Yes	Yes	Spontaneous reports by the FDA	Need planned PV/aDSM activities for new drugs or all TB drugs in NTP	Cooperation with Centers for Disease Control and Prevention (CDC) and Medical association	Include planned PV/aDSM activities for new drugs or all TB drugs in NTP guidelines; safety monitoring committee for new drugs and corresponding team in CDC
Thailand	Yes	Yes, waiting for endorsement	N/A	Low rate of PV implementation; need refresher trainings	Funding; TA	2017-2019 have local implementation training; active PV monitoring; develop regular monitoring and signal management guidelines; have on-going monitoring of implementation
Vietnam	Yes	Yes	N/A	No SOP for aDSM activities; no defined roles for each body in aDSM activities; No commitment to run aDSM from PV center and NTP	TA	In 2017, establish official committee for TB-aDSM, develop SOP and guidelines, have collaboration with NTP and PV center to make official aDSM system with defined roles and responsibilities

Recording and Reporting Structure

Country	Electronic Database	Official reporting and feedback mechanism?	Type of forms	Identified gaps	Resources needed	Goals
Burma	No	No	Paper data collection	Need to update existing data collection forms; establish official reporting feedback mechanism between NCCA, NTP, FDA; to use electronic data management system	Funding; TA; PViMS installation support if approved by FDA	In 2017, finalize aDSM data collection forms; finalize aDSM reporting flow. In 2018, explore options and identify electronic R&R systems including PViMS
China	In development	Existing experience from previous cohort studies	N/A	Need to complete database; form and train data management team at local and national level; link with CFDA AE reporting system	N/A	In 2017, continue cooperation with IT, database experts, and clinicians; identify a data manager at site and central levels; consult CFDA for proper solution for linkage
India	Available for the CEM in the Nikshay portal that's linked to the PVPi database	No, lack of two-way feedback loop to ensure two way reporting	CEM: initiation form, bimonthly report form, and DR-TB treatment card	Lack of SAE data indicators in DR-Tb quarterly data, lack of incentivized reporting; lack of hand held devices available to health care workers	Funding from national program; support from PMDT unit at national level supported thru CTB and WHO	In 2017, format reports based on feedback; include SAE data indicators in the DR-TB quarterly data; introduce hand held electronic devices for HCWs; adapt forms for aDSM to streamline more. In 2018, ensure all forms include relevant capture of data on new drugs and shorter regimen

Recording and Reporting Structure

Country	Electronic Database	Official reporting and feedback mechanism?	Type of forms	Identified gaps	Resources needed	Goals
Indonesia	Yes, e-TB manager and e meso	Mechanism from hospital to central NTP established	Paper based form for BDQ	No available form for aDSM; e-tb manager and e meso not integrated yet; limited IT staff	NTP, NADFC, GF, Partners (WHO, CTB)	In 2017, develop aDSM form; strengthen HR capacity for reporting and recording aDSM; further discussion regarding mechanism flow for RR aDSM. In 2017-2018, integrate the e-tb manager and e-meso systems; capacity building
Pakistan	Yes, Electronic Nominal Registration System (ENRS)--excel based	Reporting to PTPs & NTP but not to DRAP	Spontaneous aDSM report forms	Limited capability of ENRS, limited infrastructure capacity at central, provincial and peripheral level; DRAP & NTP doesn't have Vigiflow or other proper database for ADRs. Causality assessment, and signal detection.	PViMs package including tool and TA; resources for infrastructure development at central, provincial and PMDT site level	In 2017/2018 adaptation of PViMs at all levels needed; revise reporting forms
Papua New Guinea	Piloting eNHIS; developing the integration/ communication of PV/ADR on mSupply database system	Use WHO alert for SAE to TB program; patient history form; treatment card	2 forms	Forms lack questions about seriousness, sequel, and outcomes; only 5 provinces have been piloted; no product registration in PV mSupply; no focal point identified	Funding; TA	In 2017, gain reporting space in forms and add seriousness classification on DIPU form; collaborate with all key stakeholders for activities; identify focal person for the reporting SOP. In 2019, gradual rollout and uptake

Recording and Reporting Structure

Country	Electronic Database	Official reporting and feedback mechanism?	Type of forms	Identified gaps	Resources needed	Goals
Philippines	PViMS interoperable with Integrated TB Information System	Spontaneous reporting; study specific forms for SR and BDQ; PMDT treatment staff reports SAE to NEP with FDA	SAR; SAE paper	Health care providers non-compliant with spontaneous reporting; delayed submission of reports; FDA SAR form not comprehensive; limited infrastructure capacity at central and regional levels	Funding; TA; procurement of equipment	In 2017, DOH deputization of doctor of pharmacy public health pharmacists to help with the collection of data for causality assessments. In 2018, implementation of PViMS for SR and new drugs in all PMDT treatment facilities; expand existing infrastructure.
South Korea	Yes, web based	Responsibility for PV activity regarding new drug is up to medical facility prescribing the drug. But eligibility of new drug has been screened by "New drug committee" in CDC. Basic safety and efficacy data will be collected from May, 2017.	Nationwide basic PV activity for all drugs is being done by Korea FDA through spontaneous reports. Its process for new drugs with weak evidence of safety has been strengthened by Risk Management Plan based on regulation on duty for the last several years.	N/A	Cooperation with CDC and Medical association	Include SAEs or all AEs in web based reporting system; finalize causality assessments

Recording and Reporting Structure

Country	Electronic Database	Official reporting and feedback mechanism?	Type of forms	Identified gaps	Resources needed	Goals
Thailand	Yes, extended version of HPVC electronic reporting for active PV in TB and HPVC online database with ThaiFDA	Yes	HPVC and WHO forms	Underutilization of IT system; under reporting of PV after trainings and implementation; system in place but low performance at sites	Funding; TA	In 2017-2018, have full time coordinator for data management system; have local implementation training, record and report monitoring, and on-going monitor the implementation performance
Vietnam	N/A	N/A	N/A	N/A	TA	In 2017, design an intermediate package for aDSM for scale-up; modify current forms to meet need of aDSM plan. By 2020, develop electronic aDSM reporting; have NTP collect data, enter, and train on aDSM; have PV center perform data analysis, feedback, report, and train

Health Care Worker Capacity

Country	Health Care Worker Capacity	Identified gaps	Resources Needed	Goals
Burma	Doctors fill out 3 SAE forms; no aDSM training for HCW at all levels; new drugs and STR trainings limited	Lack training on new drugs and STR; lack funding source for in-depth causality assessment training	Funding; TA; trainings on aDSM with focus on new drugs and STR and causality assessments	In 2017, finalize SOP and training materials on aDSM; develop training module for HCW on new drugs and STR; identify funding and expert for in-depth causality assessment training (2017-2018)
China	Skilled experience on routine PV R&R	Limited awareness and experiences for aDSM of new anti-TB drugs of HCW; lack of targeted trainings	TA for causality assessment	In 2017, advocate and educate importance of aDSM; train HCW on BDQ before it's available at sites; place capacity building for aDSM from pilot to routine
India	HCWs have been trained nationally and regionally; states are preparing for cascade trainings	Huge training load training the staff at all levels; monitoring of training activities;	Funding from national program; support from PMDT unit at national level supported thru CTB and WHO	In 2017, prepare e-training material for all cadres of staff. Ongoing, plan and review training plan and plan for distribution of PMDT guidelines including aDSM plan
Indonesia	HR and training need assessment	Limited staff (number, capacity for aDSM)	NTP, NADFC, GF, Partners (WHO, CTB)	In 2017-2019, collaborate and share responsibility among clinicians, lab staff, and pharmacy staff; train clinical and AE management
Pakistan	PMDT team are providing the spontaneous PV reports	Causality analysis	aDSM officers at national and provincial levels; TA & resources for DRAP, NTP, and provincial level trainings	Train HCPs at all levels on aDSM and causality assessment
Papua New Guinea	Some capacity building activities have happened; plan for PV officer at provincial level	Need to expand capacity to regional and provincial levels; need to find PV officer	Need to look for funding beyond 2017	In 2017-2019, implement action plan for provincial MTC/PMDT committee and national PMD with PSSB for CAC with TORs and be endorsed by NTP-NDoH; capacity building; plan implementation of the strategy

Health Care Worker Capacity

Country	Health Care Worker Capacity	Identified gaps	Resources Needed	Goals
Philippines	Trained PMDT treatment staff on STR and new drugs in 6 regions; use PViMS and basic ECG included in above training.	Limited number of trainers; competing activities for trainers and participants; moratorium on training by DoH until May 2017; limited capability to conduct causality analysis at all levels of implementation	Training budget; TA	In 2017, identify and train potential trainers from the regions; conduct TOT on PMDT including STR and new drugs. In 2019, roll-out of training. In 2018, explore other training platforms and methodologies; conduct training on causality analysis
South Korea	N/A	N/A	Cooperation with CDC and Medical association	Education program for PPM nurses and physicians
Thailand	Trained TB stakeholders; TOT for DR-TB management; site staff trainings for BDQ at registered sites	Under reporting of PV even after full trainings; Lack of human resources and PV reporting awareness	Funding; TA	In 2017-2018, practical format training; In 2018-2019, incentivize activities
Vietnam	Determined need for training/additional resources; trained staff in 3 research sites (CEM)	Other sites not trained on PV yet	TA	In 2018, training on aDSM

Clinical Management

Country	Clinical Management	Identified Gaps	Resources Needed	Goals
Burma	Done at TB specialist hospitals by physicians	No system on monitoring and supervision of clinical management; limited knowledge on management of side effects of new drugs and STR at all levels; lack technical expert with extensive knowledge on new drugs and STR	Funding; TA	In 2017-2018, trainings on side effect management on DR-TB with focus on new drugs and STR at township level; develop monitoring and supervision system
China	N/A	N/A	N/A	N/A
India	ADRs managed at the PHI/Block/District at secondary/tertiary institutes	Need early identification of the ADRs by field staff; need early linking to the secondary/ tertiary centers; lack of inpatient facility at sub district level health facility	Support from national program; state level budget provisions; engagement with partners to develop model in 3 states to engage private sector in clinical management of TB	In 2018, trainings on a large scale; establish linkages with centers including private sector. In 2019, upgrade General Health System to have isolation room at sub district level health facility.
Indonesia	HR and training need assessment	Limited staff (number, capacity for aDSM)	NTP, NADFC, GF, Partners (WHO, CTB)	In 2017-2019, collaborate and share responsibility among clinicians, lab staff, and pharmacy staff; train clinical and AE management
Pakistan	6 out of 36 sites have ECG machines; all PMDT sites have audiometers; DR-TB clinical experts available and review panel are at each PMDT site	Lack of training of HCWs on aDSM	N/A	2018, train HCWs on aDSM

Clinical Management

Country	Clinical Management	Identified Gaps	Resources Needed	Goals
Papua New Guinea	SOP for PMDT including SR and new drugs	No training on SOP yet	TA-WHO & TGF	2017-2018, training of all health workers
Philippines	6 Clinical management trainings for HCW	High turnover of trained PMDT treatment staff; varying capability to manage ADRs	TA; training materials; funding	Continuous activity, conduct more clinical management training for nurses; adopt locally the clinical management training for HCW
South Korea	Centralization of DR-TB patients vs Expansion of Accessibility to medical facility	N/A	Cooperation with CDC and Medical association	Education program for PPM nurses and physicians; communication with sites with primary feedback
Thailand	DR-TB management guidelines; BDQ local implementation guidelines; DR-TB management system	Delay of regimen formulation and approval; lack of linkage between clinical management & PV management	Funding; TA	In 2017-2018, stakeholder training for TB clinical stakeholders; referral and consultancy and regimen approval process; awareness of AE recognition from current TB treatment
Vietnam	Local treatment committee in all PMDT sites; national treatment committee for new regimes; guidelines for AE management in DR-TB treatment; distant consultation meeting for difficult conditions	Lack of capacity for clinical management; inadequate practice of AE management in accordance with guidelines	TA	In 2018, continuous training specific on AE management for relevant staff; revise training module specified for aDSM

Data Management and Analysis

Country	Data management system	Electronic system	Causality assessment	Identified gaps	Resources needed	Goals
Burma	No official system at both NTP and FDA	No	N/A	Lack designated person to manage and analyze data; lack electronic data management system	FDA needs TA to establish PV policy and PV center; funding and TA for electronic data management system	In 2017, NCCA start regular data analysis and signal detection for aDSM; 2018-2019, FDA to have official PV center and designated PV person
China	N/A	N/A	N/A	N/A	N/A	N/A
India	TB program captures data in CEM-Nikshay portal	Yes, used by program for data entry	N/A	Need more capacity of program staff for data management; data output and analysis limited at state and national levels	Funding from national program; support from PMDT unit at national level supported thru CTB and WHO	In 2017, conduct ongoing skill enhancement trainings; create dashboard and export function; feedback from global database (vigiflow, aDSM); capacitate state level TB program managers to evaluate data including aDSM; evaluate data on first 600 BDQ clinical access program patients including aDSM
Indonesia	Simple data management and analysis	Yes	Conducted irregularly	Capacity for data management and analysis need to improve (increase capacity for integration data in electronic system, causality assessment, and signal detection)	NTP, NADFC; Ta for causality assessment and signal detection	In 2017-2019, conduct trainings with the help of TA; further discuss the causality assessment process; conduct routine causality assessments

Data Management and Analysis

Country	Data management system	Electronic system	Causality assessment	Identified gaps	Resources needed	Goals
Pakistan	Data collected from PMDT on monthly basis; no data analysis done; not all PMDT sites have internet and laptops	Limited	No	No current database for both DRAP and NTP for report storage and analysis; lack of proper training of staff at DRAP and NTP for signal detection; no electronic submission of data between PMDT sites and NTP and DRAP exist	TA & resources for signal detection training to DRAP & NTP staff; logistic support at NTP and PMDT sites	2017/2018, develop training package on report analysis and signal detection for the staff of both DRAp and NTP; linkage of PMDT sites with NTP to report electronically via PViMs
Papua New Guinea	Nascent	No	N/A	Early days of reporting; experiencing delayed reporting; and issue of data quality	Funding; TA	2017-2019, shift to electronic system and analyze data from paper based records; conduct trainings; roll out the electronic data management system at PMDT sites; increase communication between provincial MTC and PMDT, NTP and PSSB.
Philippines	Research teams analyzed 42 SAEs; FDA performed causality assessments for reports; FDA re-organizing PV units to help expand PV and aDSM capacity	N/A	Limited	Poor feedback mechanism on causality assessment; limited capability to conduct causality assessment; No monitoring and evaluation system	Funding; TA	In 2017, develop M&E system; 2018, DoH will mandate Pharmaceutical Division to augment FDA existing PV activities focusing only for public health programs

Data Management and Analysis

Country	Data management system	Electronic system	Causality assessment	Identified gaps	Resources needed	Goals
South Korea	Nationwide standardization of management for MDR-TB in PMDT structure: building regimen, reporting, AE management	N/A	N/A	N/A	Cooperation with CDC and Medical association	Include SAEs or all Aes in web based reporting system; finalizing causality assessments; review and analyze the collected data and feedback to NTP and PMDT program in Korea; periodic analysis of DB and secondary feedback to NTP
Thailand	HPVC online data management system and signal detection; extended version of HPVC electronic reporting for active PV in TB	Yes, but paper based data management at NTB	N/A	Lack of IT system utilization; under reporting of PV after trainings and implementation	Funding; TA	In 2017-2018, local implementation training, signal detection for AE training; record and report monitoring; on-going monitoring of implementation performance
Vietnam	Database available for CEM implementation	No	No	Lack of database structure for aDSM; current CEM database doesn't fit the aDSM requirement	TA	In 2018, design new data structure, data collection form for aDSM; integrate database

ANNEX 4

Workshop agenda

ANNEX 4

Workshop agenda

TIME	TOPIC	FACILITATION
Day One:	**Policy and Clinical Updates on New Drugs for MDR-TB**	
8:30-9:00	Registration	USAID Partner
9:00-9:20	Welcome/Introductions/Opening Remarks	Thailand MOH/TB Bureau USAID (W and RDMA)
9:20-9:35	Workshop Objectives	USAID
9:35-10:30	Status of the introduction of new drugs and USAID plans for roll out of new drugs and shortened course regimen for DR-TB treatment	USAID
10:30-11:00	BREAK and GROUP PICTURE	All
11:00- 12:30	Country Snapshot presentations: China, Burma, India, Indonesia, Pakistan, Philippines, South Korea, Thailand, and Vietnam	All
12:30-1:00	WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens	Dennis Falzon, WHO
1:00-2:00	LUNCH	All
2:00-2:30	Country Snapshot presentations: China, Burma, India, Indonesia, Pakistan, Philippines, South Korea, Thailand, and Vietnam	All
2:30-3:30	Regulators Panel: What is the role of National Drug Regulatory Authorities in introduction of new drugs?: country experiences • Thailand NDRA presentation • Philippines NDRA presentation • China NDRA presentation	Country teams to be facilitated by Janssen
3:30-3:45	BREAK	All
3:45-4.45	New TB drugs for DR-TB: Overview, clinical considerations, ethical issues, informed consent for programmatic introductions	Dr. Vivian Cox and Dr. Sein Sein Thi, Consultants
4.45-5.00	Wrap up of day one	All
Day Two:	**Essential structure of aDSM for TB care: what should it look like?**	
9:00-10:00	Designing and implementing aDSM for new drugs under programmatic conditions: Georgia Experience. Presentation and Discussion	Dr. Nino Lomtadze, Georgia, NTP
10:00-10:30	BREAK	All
10:30-11.00	Designing ADR/SAE reporting structure from patient level to local NDRA and to global level. Presentation and Discussion	Dr. Anh Innes, CAP-TB Chief of Party
10:30-11.00 11:00-12:00 12:00-1:00	Group work: country teams [NTP, NDRA, Partners and Janssen]: • Developing reporting structure of ADR/SAE reporting from patient to global level • Discussion and developing optimal model • Group presentation (gallery walk)	Country teams
1:00-2:00	LUNCH	All

TIME	TOPIC	FACILITATION
2:00-3:00	Management of SAEs data and causality analysis	Dr. Nino Lomtadze, Georgia, NTP Dr. Anh Innes, CAP-TB Chief of Party
3:00-5:00	Group work: Causality assessments	Country teams
5:00-5:30	Wrap-up of day 2	
Day Three:	**Moving forward with urgency: implementation of aDSM at country level**	
9:00-10:30	Management of new drug toxicities as part of good clinical care • Common adverse/severe events (AEs/SAEs): case reviews • Role of lab/diagnostic and clinical capacity for management of drug toxicities as part of routine care and management for MDR-TB • Gaps and recommended solutions for the existing gaps in the immediate and shorter term	Dr. Vivian Cox, Dr. Sein Sein Thi Consultants
10:30-11:00	BREAK	All
11:00-12:00	Patient safety monitoring and reporting: Recording at patient's/ facility level- proposed reporting forms (Viet Nam and Indonesia experiences)	Dr. Edine Tiemersma TB/ KNCV
12:00-1:00	Group work: Review of ADRs and SAE reporting forms on the patient/facility level from countries and recommendation for improvement and standardization	Country teams
1.00-2.00	LUNCH	All
2.00-4.00	Group work: development of country plans for aDSM implementation-next steps actions and role of each organization in the country	Country teams
4.00-5.00	Brief country presentations on next steps and Summary of the workshop and next steps	Country teams

ANNEX 5

List of participants

ANNEX 5

List of participants

NAME	COUNTRY	AFFILIATION/ORGANIZATION	POSITION/TITTLE
Country Representative			
Dr.Myat Myat Soe	Burma	Department of Pharmacology, University of Medicine 1, Yangon, Myanmar (BURMA)	Associate Professor
Dr.Khay Mar Aung	Burma	FHI 360	Technical Officer for MDR-TB and new drugs
Dr.Shin Hnaung Lwin	Burma	Department of Pharmacology Univeristy of Medicine 2	Associate Professor
Country Representative			
Dr.Gao Jingtao	China	New Drug Introduction Program Beijing Chest Hospital	Project Manager
Dr.Huang Fei	China	Chinese Center for Disease Control and Prevention	New Drug Introduction Program Focal Point
Dr.Jing Wei	China	Beijing Chest Hospital	Doctor,TB Division
Li Ling	China	FHI 360	CAP-TB China Program Manager
Zhong Li	China	FHI 360	Senior Program Officer
International Partner			
Hu Jie Qiong	China	Janssen, China	Medical Affairs Manager
Wang Xiao Chun	China	Janssen, China	Public Health Program Manager
Yao Zhang	China	FHI 360	Associate Director, Research, Global Research and Services
Country Representative			
Dr. Devesh Gupta	India	NTP	Additional Deputy Director General Central TB Division
Country Representative			
Dr. Endang Lukitosari	Indonesia	National TB Program Ministry of Health Republic of Indonesia	MDR-TB Focal Point
Dr. Harsini Hartono Sudarmo	Indonesia	Moewardi Referral Hospital, Surakarta	MDR-TB Specialist
Rahma Dewi Handari	Indonesia	NDRA	Pharmacist
International Partner			
Dr. Agtifa Primadani	Indonesia	Janssen, Indonesia	Therapeutic Area Lead - Infection Disease & Pain

Country Representative			
Dr. Abdul Ghafoor	Pakistan	NTP	Global Fund Advisor
Abdul Mateen	Pakistan	DRAP	Assistant Director Pharmacy Services
Naveed Ahmed Chaudhary	Pakistan	NTP	Senior SCM Officer
Dr. Nasir Mahmood Khan	Pakistan	NTP	National Manager
Dr. Zafar Iqbal Toor	Pakistan	NTP	National MDR-TB Coordinator
Country Representative			
Dr. Chirstopher Ope	Papua New Guinea	Physician	Eastern Highlands Provincial Hospital
Jonila Kepas	Papua New Guinea	National Department of Health	Manager, Pharmaceutical Services Standard Branch
Dr. Rendi Moke	Papua New Guinea	Physician	Port Moresby General Hospital
Country Representative			
Dr. Mary Rosary Taguinod Santiago	Philippines	NTP	PMDT Lead Coordinator
Michael Junsay	Philippines	Pharmaceutical Division, Department of Health	Representative
International Partner			
Erwin Benedicto	Philippines	Janssen, Philippines	Senior Scientific Affairs and Medical Compliance Manager
Dr.Mariquita Mantala	Philippines	TASC Project, Philippines	Technical advisor to NTP
Mehmood Anwar	Philippines	Management Sciences for Health	Country Director
Rhodesia Makahilig	Philippines	Janssen, Philippines	Local Safety Lead
Country Representative			
Dr. Kang Hyungseok	Republic of Korea	Masan National Tuberculosis Hospital, Dep. of Chest Medicine	Director
Country Representative			
Dr. Phalin Kamolwat	Thailand	Bureau of Tuberculosis	Director
Dr. Thidaporn Jirawattanapisal	Thailand	Bureau of Tuberculosis	Representative, Head of aDSM program
Dr. Petchawan Pungrassami	Thailand	Bureau of Tuberculosis	Senior Expert in Preventive Medicine
Parnpim Sutthichaya	Thailand	Bureau of Tuberculosis	CEM Coordinator
Apichest Suphannwat	Thailand	Bureau of Tuberculosis	Project coordinator
Sareeya Wethvithan	Thailand	Health Product Vigilence Centre	Pharmacist
Siwarat Namrung	Thailand	Bureau of Tuberculosis	CEM Coordinator assistant

Thawatchai Nacharajniyom	Thailand	Health Product Vigilence Centre	Pharmacist
Wimon Suwankesawong	Thailand	Food and Drug Administration	Senior Pharmacist, Expert on Drug Standards,
Yaowares Oppamayun	Thailand	Health Product Vigilance Centre	Head of HPVC
International Partner			
Nathida Cholasin	Thailand	Janssen, Thailand	Country Safety Team Lead
Salinee Vongpanich	Thailand	Janssen, Thailand	Market Access Manager
Country Representative			
Dinh Thu Huong	Vietnam	Department of Pharmacy, National Lung Hospital	Representative Department of Pharmacy
Dr. Hoang Thi Thanh Thuy	Vietnam	National Lung Hospital	PMTD lead
Dr. Nguyen Thi Mai Phuong	Vietnam	National Lung Hospital	MDR-TB program officer
Dr. Vu Dinh Hoa	Vietnam	The National Drug Information and Adverse Drug Reaction Monitoring Centre	Representative
International Partner			
Binh Mai Thanh	Vietnam	Janssen, Vietnam	Public Health Program Manager
Hoang Hai Chau	Vietnam	KNCV	Technical Officer
Dr. Nguyen Thien Huong	Vietnam	Challenge TB/KNCV	Challenge TB and KNCV Country Director
Trang Nguyen Le Minh	Vietnam	Janssen, Vietnam	Medical Affairs Manager
International Partner			
Dr. Anh Innes	Asia Pacific region	FHI 360	Chief of Party, USAID CAP-TB Project
Ross Underwood	Global	Janssen, Global	Global Access Leader
Dr. Md Khurshid Alam Hyder	India	WHO/SEARO	Regional Advisor (TB) WHO/ SEARO
Dr. Edine Tiemersma	Netherlands	KNCV	Senior Epidemiologist
Dr. Geraldine Hill	New Zealand		Consultant
Dr. Lungten Wangchuk	PNG	WHO/PNG	Medical Officer
Dr. Chrispin Kambili	USA	Johnson & Johnson	Global Medical Affairs Leader

USAID			
Dr. Sein Sein Thi	Burma	USAID/Stop TB Consultant	MDR-TB Clinical Consultant
Dr. Nino Lomtadze	Georgia	USAID/Stop TB Consultant	MDR-TB Clinical Consultant
Dr. Tamar Gabunia	Georgia	USAID/Stop TB Consultant	MDR-TB Clinical Consultant
Dr. Amar Shah	India	USAID/India	Project Management Specialist (Tuberculosis Care & Control)
Tito Rodrigo	Philippines	USAID/Philippines	Project Management Specialist
Dr. Vivian Cox	USA	USAID/Stop TB Consultant	MDR-TB Clinical Consultant
Dr. Inoussa Zabsonre	USA	USAID/Stop TB Consultant	MDR-TB Clinical Consultant
Dr. Edmund Rutta	USA	USAID/W	Senior TB Technical Advisor Infectious Disease Office/ Tuberculosis Division Global Health Bureau
Dr. Alex Golubkov	USA	USAID/W	Senior TB Technical Advisor
Carolyn Rhodebeck	USA	USAID/W	MDR-TB Intern

Endnotes

1 "Bedaquiline Donation Program Asia Regional Pharmacovigilance (PV) Workshop: Implementation of active TB drug-safety monitoring and management (aDSM) for New Drugs and treatment regimens for MDR-TB", presented by Dr. Edmund Rutta, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand.

2 "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand; "National Action Plan for Combating Multidrug-Resistant Tuberculosis, Year One Report", USAID, Accessed at: https://www.usaid.gov/sites/default/files/documents/1864/NAP-for-Combating-MDR-TB-Year-One-Report-508-v10.pdf.

3 The regimen composition: 4-6 Km-Mfx-Pto-Cfz-Z-Hhigh-dose-E / 5 Mfx-Cfz-Z-E.

4 "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand; and "The Shorter MDR-TB Regimen, World Health Organization, May 2016, Accessed at: http://www.who.int/tb/Short_MDR_regimen_factsheet.pdf

5 "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand.

6 "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand; "Programmatic introduction of newer drugs for drug-resistant tuberculosis: Overview, clinical considerations, ethical issues, and informed consent", presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 25 April 2017, Bangkok, Thailand; USAID's Bedaquiline Donation Program in Partnership with Johnson and Johnson, Accessed at: https://www.usaid.gov/what-we-do/global-health/tuberculosis/technical-areas/bedaquiline-donation-program.

7 "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand.

8 "DR-TB Drugs Under the Microscope: Sources and Prices for Drug-Resistant Tuberculosis Medicines", Third Edition, Médecins Sans Frontières and the International Union Against Tuberculosis and Lung Disease, October 2013, Accessed at: http://apps.who.int/medicinedocs/documents/s21068en/s21068en.pdf.

9 "Designing an ADR/SAE system: from the patient to national and global levels", Dr. Anh Innes, FHI 360 Chief of Party, Control and Prevention of Tuberculosis Project, Clinical Assistant Professor of Medicine (Adjunct), University of California San Francisco (taken from "The Importance of Pharmacovigilance: Safety Monitoring of Medicinal Products, World Health Organization, Geneva), 26 April 2017, Bangkok, Thailand.

10 "Essential medicines and health products: Pharmacovigilance", World Health Organization, Accessed at: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/.

11 "Introduction to PV: application for roll out of new drugs and shorter treatment regimen for DR-TB treatment", presented by Dr. Alexander Golubkov, Senior TB Technical Advisor, USAID, 25 April 2017, Bangkok, Thailand; "WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens", presented by Dennis Falzon, WHO/HQ Global TB Programme, Geneva 25 April 2017, Bangkok, Thailand; "Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation", World Health Organization, 2015.

12 "WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens", presented by Dennis Falzon, WHO/HQ Global TB Programme, Geneva 25 April 2017, Bangkok, Thailand.

13 "WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens", presented by Dennis Falzon, WHO/HQ Global TB Programme, Geneva 25 April 2017, Bangkok, Thailand; "Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation", World Health Organization, 2015.

14 "WHO recommendations on active drug safety management and monitoring (aDSM) for new drugs and regimens", presented by Dennis Falzon, WHO/HQ Global TB Programme, Geneva 25 April 2017, Bangkok, Thailand.

15 "Designing and implementing aDSM for new drugs under programmatic conditions: Georgia experience", presented by Dr. Nino Lomtadze, USAID/Stop TB Partnership MDR-TB Clinical Consultant, Head of Surveillance and Strategic Planning Department, National Centre for Tuberculosis and Lung Diseases (NCTLD), Georgia, 26 April 2017, Bangkok, Thailand.

16 "Management of SAE data and causality analysis", presented by Dr. Nino Lomtadze, USAID/Stop TB Partnership MDR-TB Clinical Consultant, Head of Surveillance and Strategic Planning Department, National Centre for Tuberculosis and Lung Diseases (NCTLD), Georgia, 26 April 2017, Bangkok, Thailand.

17 "Causality Assessment: Prep for Group Work", presentation by Anh Innes, FHI 360 Chief of Party, Control and Prevention of Tuberculosis Project, Clinical Assistant Professor of Medicine (Adjunct), University of California San Francisco, 26 April 2017, Bangkok, Thailand.

18 "Causality Assessment: Prep for Group Work", presentation by Anh Innes, FHI 360 Chief of Party, Control and Prevention of Tuberculosis Project, Clinical Assistant Professor of Medicine (Adjunct), University of California San Francisco, 26 April 2017, Bangkok, Thailand.

19 "Management of new drug toxicities as a part of good clinical care", presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 27 April 2017, Bangkok, Thailand.

20 "Roadmap: from pilot project or research to country-wide implementation", presented by Dr. Edine Tiemersma, KNCV Tuberculosis Foundation, 27 April 2017, Bangkok, Thailand.

21 "Management of new drug toxicities as a part of good clinical care", presented by Dr. Vivian Cox and Dr. Sein Sein Thi, MDR-TB Clinical Consultants, 27 April 2017, Bangkok, Thailand (taken from endTB Clinical and Programmatic Guide for Patient Management with New TB Drugs, Version 3.3. http://endtb.org/sites/default/files/2017-02/endTB%20Clinical%20Guide%20v3.3_0.pdf.

Bedaquiline Donation Program

Asia Regional Pharmacovigilance Workshop: Implementation of active TB drug-safety monitoring and management for new drugs and treatment regimens for multidrug-resistant tuberculosis

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